Paul G. King's
Formal Comments

Monday, 12 April 1999

Dockets Management Branch (HFA–305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 99N-0386

FORMAL COMMENTS ON:

Docket Number	**: 99N-0386**
Comments On	**: Talking With Stakeholders About FDA Modernization; Notice of Meetings and Teleconference**
Pursuant To	**: An FDA "request for comments" promulgated within the FDA's GGP (62 FR 8961, February 27, 1997)**
In	**: *Federal Register*, 64(54), 13804-52277, Monday, March 22, 1999**

The formal comments on the pages following this one address the questions proposed by the agency pursuant to the aforementioned notice and request for comments.

Should any clarification be needed of any comment or any reviewer find any factual error in what has been said, then I would be happy to attempt to address the issues raised provided they are furnished to me in writing.

Sincerely yours,

Paul G. King, Ph.D. 12 April 1999

99N-0386

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INITIAL COMMENTS

Before addressing the questions on that the agency is seeking input, let me pose and cryptically answer three rhetorical questions and the apparent general answer that the agency seems to be giving its stakeholders today.

1. What is more important than ensuring that drugs and drug products are safe and **not** adulterated?

   Priorities.

2. Why is it that the FDA permits **deliberate** noncompliance by any drug or drug product manufacturer that it is charged with regulating and allows drug product that it knows to be adulterated under **21 *UCS* 351(a)(2)(B)** to remain in commerce without at least seeking the maximum civil penalties that it can?

   Because ...

3. Why is it that many agency personnel in both review and compliance seem not to know, much less understand, either statistics or the explicit requirements of the regulations that they are charged with enforcing?

   Because assuring personnel competency in these areas has not been an agency priority.

RESPONSE TO FDAMA STAKEHOLDER'S QUESTIONS

1. Science based decisions are made throughout the life span of products from initial research, development and testing, through production, marketing, and consumption. These decisions require the best science to identify, evaluate, and balance product risks and benefits. It is crucial that FDA, in collaboration with product sponsors, develop a shared understanding of new science and technologies and their effect throughout a product's life span.

   Agency Question:

   What actions do you propose the agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision making?

   A Concise Answer:

   Before attempting to expand, the FDA first needs to establish that its personnel are fully competent in statistics and analytical science as well as in the requirements of the CGMP regulations that those personnel administer.

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Explanation Of Concise Answer:

The Importance Of Knowing And Understanding Statistics

Until the agency is equipped to ensure that fundamentally sound science is being presented and incorporated into the documents being submitted to the agency, the agency should cease attempting to make risk-based decisions about drug products. But Dr. King, surely the agency ensures that the submissions it receives meet the minimum requirements of sound and appropriate science. Surely the agency personnel who are involved in reviewing the documents filed with the agency, those who inspect, and those who make decisions understand the required fundamentals of sound science. Don't they?

Sadly, my experience with FDA personnel at all levels above the secretarial level (inspectors/investigators/compliance officers/administrators/experts) is that many of them freely admit that they do not truly know — much less understand — the fundamentals of the science upon which all safety, efficacy, quality, and risk decisions are made. Even though that science, statistics, must be properly used to substantiate all specifications, release criteria, sampling plans, test methods, and any other extrapolation from the results or outcomes observed to the general population (batch or lot, method or test procedure), most of the FDA personnel seem to lack the level of understanding of statistics required for them to critically assess the information being provided by manufacturers and their consultants.

To understand statistics, one must understand probability, randomness, representativeness, sampling, distributions, confidence levels, uncertainty and the proper apportionment of risk. Unfortunately lacking sufficient understanding of all the preceding, those that do not understand the fundamentals of statistics are reduced to accepting much of what is stated regardless of its fundamental validity instead of questioning or checking the validity of the assumptions, approximations, approaches, supporting statements and conclusions presented to them in the "scientific" documents presented to them. Though many examples could be cited, a few should do.

Though the regulations for drug products require that the sampling and testing plans be scientifically sound, the agency has approved numerous ANDA and NDA applications in which, without any proof of scientific soundness, the sampling plans for the raw materials sample the "$\sqrt{n}+1$" containers, validation protocols only address 3 validation batches, the sampling plan for in-process and release sampling is either not presented or is defective, and the release testing plan uses the USP monograph, or a subset thereof, even though the USP warns against such in its ***General Notices***, "(c)onfusion of compendial standards with release tests and statistical sampling plans occasionally occurs" and further states "manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until the expiration date, when stored as directed.."

Moreover, though all samples tested by the manufacturer are **required** in **21 *CFR* 211** to be tests upon **representative** samples, the sampling and testing plans submitted often provide little, or **no**, proof that the samples being tested are truly representative of the batch or lot from which they were taken.

Lacking the requisite knowledge, the agency has "relied" upon industry to provide compliant submissions.

Knowing that the agency lacks the ability to critically evaluate the scientific soundness of the information being provided, the industry, as a whole, has chosen to use approaches that are not

scientifically sound and present them couched in pseudo-science. For example, although the USP explicitly states in its ***General Notices*** that the number of units specified in a compendial monograph or general chapter is a **minimal** figure that is "chosen only for the convenience of analytical manipulation" and that the quantity or number specified "is not intended to restrict the quantity of substance or number of units ... that should be tested in accordance with good manufacturing practices," the industry has often improperly chosen to use the USP quantity or numbers in its internal testing programs.

Worse still, even though the USP number is a **minimum** number, some firms have elected to test less than that minimum number. For example, at the recent **23rd International GMP** conference, one firm's presentation showed that 10 units, without any requirement that the units be chosen in a manner that assured they were representative, were being tested for Assay when the USP minimum is 20 units. Furthermore, applying simple statistics, the scientifically sound minimum number for an Assay is about **67 representative units** if the result is to be within 1 % of the true batch mean.

Similarly, although the CGMP regulations for drug product batch release explicitly require **(21 *CFR* 211.165(d))**[10] the use of "appropriate statistical quality control criteria as a condition for their approval and release," the agency, apparently lacking any understanding of this requirement or else deliberately ignoring it, currently allows firms to have batch release systems that do **not** comply with this requirement.

Thus, if a firm chooses to release a batch of 10,000,000 units based on testing a few non-representative units (10 for Assay, 10 for CU, 10 for Dissolution or Drug Release, *etc.*) and finding that the results are inside of the USP's lifetime criteria, the agency permits the firm to do so even though doing so does **not** meet the explicit requirements of **21 *CFR* 211.165(d)**. So much for the CGMPs being the minimums below which a firm may **not** operate.

Examples Of Statistical Pseudo-Science

Dr. King, you assert that some in the pharmaceutical industry are promulgating pseudo-science. Could you provide an example? An example, you say.

Well, for one, in 1997, the Parenteral Drug Association (PDA) published a white paper titled ***Technical Report No. 25***, "Blend Uniformity Analysis: Validation and In-process Testing." This report attempts to attribute or derive statistical validity to the USP's compendial test numbers in spite of the fact that the USP imposes **no representative** sampling criterion on the compendial sample numbers and explicitly represents them as being "chosen only for the convenience of analytical manipulation." Attempting to represent non-statistically based numbers as having a statistical basis or statistical implications certainly appears to be pseudo-science. Especially, when USP's compendial numbers apply to finished dosage units and the report is attempting to apply them to powder samples from "uniform" dry-powder blends.

Further, this report attempted to convince the agency to ignore the requirements of **21 *CFR* 211.110** by presenting how hard it is to take unit-dose samples from blends of powders as somehow justifying their position that they need **not** comply with **21 *CFR* 211.110**. Since when is difficulty a scientifically sound defense for noncompliance?

Moreover, certain firms have apparently taken the PDA's positions to heart and ceased doing the requisite in-process testing mandated by **21 *CFR* 211.110** for mix uniformity. Though the agency is aware of some of these firms, it has, to my knowledge, taken **no** definitive action to ensure that those firms comply in this area.

Furthermore, I provided a formal critique to a member of the committee that prepared the PDA report in the later half of 1998 (when was able finally to get a copy of it to review), that member assured me that copies of it had been provided to all members of the committee, and a copy of my formal evaluation (included as **Appendix A** for those who wish to be able to evaluate my comments for themselves) was also provided to the FDA. To date **no** member of the PDA has gotten back to me with any scientifically sound evidence overcoming any of the issues raised **nor**, to my knowledge, has the FDA moved to sanction those firms that it knows, or should know, are deliberately operating in a manner that does not comply with **21 *CFR* 211.110**.

In another example, a statistician for a major drug firm faced with a real, but unwanted, bimodal powder filling distribution for a new drug product intended for pediatric use simply regrouped the data until the distribution appeared to be monomodal knowing that the reviewer would probably **not** catch his unscientific manipulation of the data.

When this problem was brought up, it was "acknowledged," but the powder filling set point was still established using the distorted data as the basis and **no** appropriate overage was added to assure that each "unit of use" bottle provided sufficient drug product. Subsequent "real world" post-approval filling experience confirmed that a significant percentage of bottles had a fill weight that provided lass that the claimed level of the active in each dose.

In some cases, a combination of low fill weight and blend uniformity combined to give bottles with significantly less that the labeled volume. However, because batches were passing the USP's Deliverable Volume minimums, the batches were released even though the results from the few samples tested predicted that more than "5 %" of the bottles in the batch could be deficient in volume and that less than "85 %" provided "not less than the label claim of active" at release — they did meet the USP's lifetime range.

What Should Be Done Immediately?

1. All FDA personnel involved directly or indirectly in the evaluation of data or in the assessment of compliance with CGMP, GLP, GCP, etc. need to demonstrate their understanding of and competency in application of the fundamentals of statistics, probability, confidence, and distributions. To assure that all such personnel have the requisite knowledge and can use it properly, the agency needs to periodically assess (by suitable testing) the competency of all such personnel and provide training or remedial training for all those who fail to meet minimum competency standards. Those who, after repeated training and retraining, fail to meet the minimum competency standards should be placed in positions where this competency is not required or, if no such positions are available, outplaced.
2. Until an adequate number of agency personnel are qualified and found to be competent, all decisions involving statistics should be reviewed by those who are competent in statistics. If insufficient agency personnel are found, then qualified consultants and academics should be included as members of the review groups.
3. Where recognized national and international <u>statistical</u> standards exist (such as ***ANSI/ASQC Z 1.4*** and ***Z 1.9*** or ***ISO* 3951**), the agency should **a)** mandate that these are the minimums for compliance and **b)** require that any alternative that be proven to provide a higher degree of consumer protection before allowing it to be used.

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The Importance Of Knowing And Understanding Analytical Science

To understand analytical science, one must know and understand sampling, error analysis and uncertainty, test procedures' strengths and weaknesses, what is scientifically sound, and what are the scientific prerequisites for a given analysis (for example, UV Assay) or examination technique (for example, NIR sample classification). In addition, in testing, many do **not** seem to understand the fundamentals of sample analysis that are required for them to make scientifically sound decisions concerning the information being gathered and presented in this area.

For example, even though two (2) levels of standard is the scientifically sound minimum number of levels required for a comparative analysis of samples when the analytical response (r) is related to the amount of analyte (x) by a linear relationship that has a significant **non-zero** intercept (for example, $x = 10000\ r + 1000$), the agency (and apparently the USP) continues to accept and permit the use of a single standard in such methods.

Worse still, I have seen cases where approvals were obtained based on submissions containing a method that any competent analytical chemist would have recognized as being a scientifically unsound method or cases where approvals were obtained in which the sampling plans, the specifications, or both were scientifically unsound or inappropriate or non-complying or all three.

In another clear example of the agency's lack of understanding of how to assess the appropriateness of a testing approach, the agency continues to recommend that "in house" standards be assessed by assaying them using HPLC against the USP Reference Standard (provided the USP Standard exists) even though the overall analytical uncertainty of the HPLC method's that are typically used (on the order of 2 % [at the 1-RSD level]) renders any test result essentially meaningless. In the simplest case, presuming that: **a)** the USP Reference Standard has an assigned "as is" value of 100 % and **b)**, contrary to reality, a true 100-% value is possible, the agency accepts a 100.1 % value for an in-house standard found using a comparative "2 % (1-RSD)" HPLC test procedure instead of rejecting the approach because, at the 3-SD level [about 99.97 % of the population], the comparative result value of "100.1 % is uncertain by at least "2 %" and, from a scientific viewpoint, is somewhere between "94 % and 106 %."

Furthermore, when such comparative testing is <u>not</u> done, the agency tends to consider the firm's standardization program deficient. Thus, most firms perform the comparative test (and some even use the value) even though the result is **not** accurate enough to be used to assign a value to an in-house standard. [The scientifically sound approach for assigning a purity value to an in-house reference standard material is to determine the weight percentages for all of the impurities in the candidate in-house material (either singly or as a whole) and subtract the impurities and their uncertainty values from 100 % by weight.]

Similarly, the FDA, industry, and even the USP continue to push the use of questionable HPLC methods in cases where the use of other methods is equally, or more, scientifically sound. Moreover, instead of mandating that all validated methods have rigorous factor studies and established tolerances for all controllable factors, the agency, encouraged by industry, is attempting to get a consensus on "rules of thumb' for how much a given parameter can be adjusted before the method is "modified." Scientifically, if no explicit adjustment ranges are provided, them any "adjustment" is, by definition, a modification of the method!

Finally, the issue of test result uncertainty is usually completely ignored (as in the comparative HPLC method for evaluating in-house standards) or **not** given appropriate status in evaluating the scientific soundness of the analytical approach used. [This leads to HPLC results being reported as 102.4 % of the label claim (based on 2 injections of a single sample preparation) when the average RSD

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for 5 injections of the "100 % standard was 1.5 %, the use of a single level of a standard is not valid, and, because uncalibrated volumetric glassware was used for the preparation of the samples and the standards and different analysts prepared the sample and the standard, the overall 1-SD preparation and test error can easily exceed 3 %. The reality is that the sample value is, at best, "$102.4 \pm 3.3_5$ % of label claim."]

Moreover, the USP has taken (and the agency has **not** objected as it could and should) the scientifically unsound position that an HPLC or other Assay test result value of 89.951 % of label claim can be validly rounded up to "90.0 % of label claim" and "pass" while a result value of 89.949 % of label claim **cannot** be rounded up (the USP says this one is "89.9 % of label claim" and that it "fails") when, even forgetting the test procedure uncertainty, the measurement uncertainty is on the order of 0.5 % to 1.9 % at the 1-RSD level.

What Should Be Done Immediately?

1. All FDA personnel involved directly or indirectly with analytical test or examination methods should be required to have demonstrated competence a) as analytical chemists, and b) in understanding the uncertainties, strengths and weaknesses associated with any and all analytical techniques (quantitative, semi-quantitative and qualitative). [They should understand and be able to estimate the uncertainty in any computed value as well as identify the sources of error in the result values obtained by any procedure.]

   To assure that all such personnel have the requisite knowledge and can use it properly, the agency needs to periodically assess (by suitable testing) the competency of all such personnel and provide training or remedial training for all those who fail to meet minimum competency standards. [Those who, after repeated training and retraining, fail to meet the minimum competency standards should be placed in positions where this competency is not required or, if no such positions are available, outplaced.]

2. Until an adequate number of agency personnel are qualified and found to be competent, all decisions involving analytical procedures should be reviewed by those who are competent in the are of analytical procedures. If insufficient agency personnel are found, then qualified consultants and academics (both having, at a minimum, a masters degree in analytical chemistry, or an equivalent, and demonstrated competency by examination) should be included as members of the review groups.

3. Until recognized national and international standards exist that define the error sources and uncertainties for a given analytical procedure and provide a scientifically sound definitive approach to the use of a given analytical procedure, the agency should mandate that all users of a method **not** only **a)** develop or verify a developed method in full compliance with the applicable ICH guidelines but also **b)** define, measure and track the uncertainty associated with any value measured using a given analytical test procedure, and **c)** require that the uncertainty in any value be appropriately used in determining whether or not a material is acceptable. [As corollaries, **a)** no final quantitative result value should be allowed to be expressed to more than one figure beyond the least significant figure; **b)** if the permitted extra digit is expressed to require it to be expressed in a typeface that is no larger than $^2/_3^{rds}$ the size of the typeface for the least significant figure; and **c)** no rounding of the calculated numerical values should be permitted.]

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The Importance Of Knowing And Understanding CGMP

As the preceding discussions indicate, it would seem that agency personnel need to know and understand the statutes, regulations, standards and guidance that governs the industry that they regulate. However, as the preceding examples indicate, many in the agency do not understand the requirements of the statutes and regulations that are required for them to be truly competent in competently discharging their assigned duties.

Without an adequate knowledge and understanding of the statutes, regulations, standards and guidance that governs or, should be governing, their actions, agency personnel are left to make assessments and decisions based on their admittedly flawed knowledge and understanding. Moreover, realizing this lack and, in some cases, exploiting it, the pharmaceutical industry has been able to get the agency to essentially ignore certain "onerous" requirements in **21 *CFR* 211** and related regulations.

At a minimum, the overall effect has been to allow the industry to produce products whose quality and safety is less than it should be.

For example, though **21 *CFR* 211.101(a)** requires that the "batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient," I have personally seem cases where the agency approved drug product ANDA's where the drug product data submitted clearly demonstrated that the drug product was not so formulated. In some cases, this deficit was supported by years of annual review data having an Assay mean of about "98 % of the label claim."

Similarly, the reality is that the CGMP regulations for drug products clearly mandate in-process monitoring and validation of **each batch "for those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**." Yet, though several drug product manufacturers freely admit that they do **not** do any blend testing for mix uniformity for each routine batch manufactured, they continue to receive FDA approvals and their existing products are allowed to continue to be manufactured below the floor established by the CGMP regulations.

What Should Be Done Immediately?

Unfortunately, there are no FDA regulations (comparable to **21 *CFR* 211.25** or **21 *CFR* 820.25**) that compels the agency to train their personnel in CGMP or to prove that their personnel have the requisite competency in any area. To address this, I would propose that either regulations or changes to the appropriate statutes be made that mandate that the FDA be competent. For example, adoption of regulations that read as follows:

xx CFR mmm.nn Personnel qualifications.

"(a) Each FDA employee engaged in regulating the review, approval, manufacture, processing, packaging, labeling, packing, holding, testing, and quality control of a product or device shall have education, training, and experience, or any combination thereof, to enable that person to perform their assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including all applicable current good manufacturing practice regulations as well as the written procedures required by those regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees are competent in this area and remain familiar with CGMP requirements applicable to their assigned functions.

(b) Each FDA employee responsible for supervising those engaged in regulating the review, approval, manufacture, processing, packaging, labeling, packing, holding, testing, and quality control of a product or device shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the product or device being regulated has the safety, identity, and quality (as well as strength, quality, and purity for drugs and drug products) that it purports or is represented to possess.

(c) There shall be an adequate number of qualified agency personnel to perform and supervise the regulation of the review, approval, manufacture, processing, packaging, labeling, packing, holding, testing, and quality control of each product or device."

What Assistance Have You Provided To the Agency To Address The Issues You Have Raised?

Lest I be accused of pointing to the problem without providing scientifically sound solutions to the problems areas presented, I have attempted to provide both the agency and the pharmaceutical industry with robust solutions.

In attempting to address apparent deficiencies in statistical understanding, I have personally prepared and submitted more than half a dozen white papers [1-7] designed apply fundamentally sound science, including statistics, in a manner that fully complies with the existing laws (statute and regulations) with respect to key issues in the drug and drug products area.

Further, at the verbal request of the agency, I have prepared and submitted a white paper[8] to the agency that outlines and establishes one scientifically sound and appropriate approach to the development of methodology for the scientifically sound quantitative inspection (sampling and testing) of drugs and drug products. That white paper addresses the development of scientifically sound and appropriate inspection (sampling and testing) methodology for the analysis of drugs and drug products.

In every case, the white papers have explicitly addressed the applicable statutes, regulations, standards and guidances that bear on the area or areas being addressed.

Additionally, when I have seen scientifically unsound papers published, I have notified the authors, the publishers, the appropriate office division within the FDA, and knowledgeable colleagues, in writing, of the problems in the articles and asked any and all to correct me if any of the issues that were raised were incorrectly presented. Further, after seeing many scientifically unsound analytical testing procedures being accepted by both the FDA and USP, I have recently published[9] a valid approach to developing comparative test methods that can validly use a single standard or a single titrant standardization level. [For existing methods, that approach can be used to determine the analysis range, if any, over which the use of a single standard is scientifically sound and, if two standard levels are required, determine where the two standard levels should be.]

Furthermore, many of my suggestions to improve the scientific soundness of the USP have been published in the USP's ***Pharmacopeial Forum*** in 1998 with the hope that better science be incorporated into USP 24 (due to be published in mid-1999 [effective January 1, 2000]).

What Should Be Done Until The Issues Raised Are Addressed?

Until the requisite competencies can be established for each FDA employee above the secretarial level, those employees lacking competency should have, at most, limited participation in any decision making. If the agency finds that it does **not** have competent personnel in a given area who understand both the requisite science and CGMPs, then they, like many in the industry,

need to hire competent consultants who can provide the critical evaluation of submissions that is currently lacking and who can train agency personnel until they are competent.

Furthermore, rather than accepting the industry's positions, the agency needs to demand (as it should have been doing all along) that each submission provide, or reference, the submitting firm's scientifically sound rationale, based on recognized statistical standards and reference texts, for all the specifications, inspection (sampling and testing, or examination), and release criteria in all of their existing submissions as well as in each new submission. In no case should the agency continue to allow any violative or scientifically unsound "industry practice" to continue.

2. As the agency attempts to meet its public health responsibilities, the speed of discovery results in an avalanche of new information from government, academic, and industry scientists.

Agency Question:

What actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities throughout a product's life cycle?

A Concise Answer:

To facilitate the exchange and integration of information, the FDA must make certain that:

a) Agency personnel who are involved in "integrating" scientific information are competent in statistics as it applies to the scientific assessment of the scientific information and

b) The information provided is accurately presented in an appropriate statistically valid, scientifically sound, unbiased format that reveals the inherent uncertainty and confidence limitations in the information being exchanged or integrated.

Explanation Of Concise Answer:

The explanation of part **a)** of the "Concise Answer" is reflected in the responses provided to the agency's first question.

For part **b)**, the FDA needs to mandate that:

1. **Whenever a recognized appropriate scientifically sound standard exists,** the agency should require:
   - **a)** The scientifically sound, appropriate, recognized standard(s) **must** be used;
   - **b)** **All** scientific information provided **must** be derived from the proper application of the appropriate recognized standard(s) (ANSI/ASQC [formerly MilSpec], ISO, ICH, IEEE, IEC, *etc.*);

   and

   - **b)** **Proof of appropriateness and compliance** with said standard(s) **must** be submitted.

2. **Where no recognized scientifically sound minimum standards exist**, the agency should require that the submission of a detailed, step-by-step proof document that clearly establishes the scientific soundness of the approach used by the company to satisfy the requirement.

The preceding requirements should apply to all inspection (sampling and testing, or examination) plans, test or examination procedures, requirements, specifications, and acceptance or rejection criteria

Furthermore, the agency should impose stiff penalties for any fraud (including automatic refusal to approve a new product or, if approved, revocation of approval) with respect to compliance with the above.

If such were required, not only would the amount of time required by the agency to understand the uncertainty in, and the import of, the information provided be reduced, but the quality of the drug product taken by the end user would be improved.

Moreover, adopting and rigorously enforcing such policies would reduce the incidence of scientifically defective filings. In turn, the reduction in the incidence of scientifically defective filings could reduce the filing burden on the agency while, hopefully, improving the safety and quality of the drug products being made available to the consumer.

3. Most products in the American marketplace, especially medical ones, have two facets. On one side they benefit users and often improve lives. They are, however, rarely without risk, and their use can result in known and unknown side effects. Consumers must weigh benefits and risks before using these products, often times with incomplete information.

Agency Question:

What actions do you propose for educating the public about the concept of balancing risks against benefits in public health decision making?

A Concise Answer:

The current reality is that most of the recent increase in direct-to-the-public advertising (see Appendix B) has been increasingly misleading (see the FDA's 1998 and 1999 "Warning Letters"). Clearly, the drug product companies are more interested in influencing, rather than educating, the public.

To stop this, <u>all</u> direct-to-consumer <u>advertising</u> of drug products (including the offering of rebates or a free trial to the patient as an inducement to try a particular product) should be restricted to advertising that:

a) Educates without attempting to influence and

b) Provides complete disclosure of <u>all</u> of the known benefits and risks, including the comparative ones, of their products for <u>all</u> of its approved uses.

If the agency truly wishes to educate the public in the risks and benefits of various drug products, then it should publish, make available

to the public for a nominal fee, place on the Internet, and distribute to every library, an authoritative monograph on each drug product (like the ones in Mosby's GenRx) with appropriate updates that highlights the comparative risks and benefits of various categories of medicines. In addition, it should require that all drug product be dispensed with the manufacturer's name, product name, NDC number, and lot number clearly visible.

Finally, it should start a grass roots educational program to have every one who is able (and their health care provider, if they are not) provide feedback through local toll-free numbers or online (using the NDC and lot numbers) any complaint about a product. The drug-product information provided (manufacturer, drug product name, NDC number, strength, lot number, and complaint and, where available, the cause(s) of the complaint and, if known, the action taken by the manufacturer to address the complaint [stripped of all patient and provider data]) should be maintained in an online central database that is available to the public.

To assure that the consumer receives the requisite information, the agency needs to issue federal regulations that mandate that, at a minimum, any drug product provided or administered to a patient must be provided with the manufacturer's name, the name of the product, its NDC number, the strength of the drug product, the lot number of the drug product and, if any, its expiration date to assure that the requisite information is provided. [Currently, dispensing is controlled by the states and their regulations often fail to mandate that the lot number of the drug product be provided.]

To pay for this activity, the agency should ask Congress to appropriate funds to support this activity.

Explanation Of Concise Answer:

As is apparently the case in many instances, the agency begins with a flawed premise — in most cases, "health care providers" and not the patient are weighing the risks and the benefits with many being as, if not more, concerned about cost containment rather than the patient per se. Thus, the public needs to demand that the manufacturers and the health care providers provide each patient with medical care that weighs that patient's side-effect risks against that patient's effect benefits. The public needs to be educated to the fact that their "health care provider," hopefully a doctor, needs to care, or be induced to care, about the patient for whom the choices are being limited or restricted on an ever-increasing dollar-cost basis with less and less concern for the individual patient's risks and benefits.

If the agency finds that commercial advertising by the manufacturer is necessary, then the agency should mandate that **all** the risks, including those related to lack of patient experience with the product, be presented immediately after (and in the same size type as or voice or visual-effect level as) the purported benefits of the drug product. The agency and Congress need to remember that the agency should have only one mission — to protect the public. [If Congress

truly believes that the government should be assisting drug manufacturers, then it should create a separate agency for that function and cease trying to turn the FDA into an "Industry Support Agency."]

Having been bombarded by the industry's current efforts to "educate" the "consumer" after the FDA loosened the restrictions on such advertising in 1997, it is clear that the industry is more interested in influencing us to buy their product rather than educating us. One need only consider the recent report **(see Appendix B)** on the increase in direct-to-consumer advertising that clearly demonstrates that the FDA's loosening of the rules on advertising has led pharmaceutical manufacturers to attempt to influence, rather than educate, the consumer. Moreover, given the recent rise in the number of FDA warning letters, and their content, the industry seems to be increasingly flouting the existing rules — indicating that the agency's current controls are, at best, ineffective.

To combat company advertising abuses, the FDA needs to implement an administrative "fines" structure designed to punish those who repeatedly violate the agency's regulations in this area. To facilitate this, Congress should **a)**, if necessary, provide the requisite enabling legislation and **b)** direct that the moneys derived from such fines be earmarked to the agency for use in educating the public. If administrative fines are deemed inappropriate, then repeat violators should have all their pending product filings put of hold for a period of **not less than**: 30 days for the first offense, 60 days for the second offense, 180 days for the third offense, and 1-year for all subsequent offenses with a provision for the suspension to carryover to any firm that acquires or merges with a firm having the hold apply to all the submissions of all parties. Additionally, if the firm has no pending filings, the hold period should commence with on the date of the next filing of the firm. To reward those who act responsibly or improve their compliance status, one of the firm's offense should be expunged for each year of non-violative compliance following the last incident.

Further, if the agency truly wishes to educate the public concerning the drug products it regulates, it needs to provide the public access to the problems with drug products as they occur. Ideally, the agency needs to provide a public accessible real-time database containing all complaint and Field Alert information concerning the drug products in commerce as that information comes to the agency.

To combat the delay in issuing Field Alerts that exists and that this action might exacerbate, the agency needs to adopt a similar fines or holds plan as that outlined for advertising noncompliance.

Were such a database to be available and complaint reporting encouraged, not only would the consumer be better educated about the risks of a particular drug product or lot thereof, but the information provided should also enable the agency to: **a)** spot manufacturer, product, and batch-related problems from widely divergent areas more quickly; **b)** assess the problems in a near real-time action frame; and **c)** more rapidly respond when it deems corrective action is needed. Moreover, because no individual patient information would be asked for or entered into the database, it should be free of "patient privacy" concerns.

Finally, the support of this database should be funded and audited by Congress as a separate item to assure that the agency has the funds it needs, maintains the database as it is supposed to, and rapidly responds to the concerns raised by the public.

4. The agency stated in the "FDA Plan for Statutory Compliance" that inflation has eroded real assets that can be applied to meet its public health mission while Congress has increased its responsibilities.

Agency Question:

Because the agency must allocate its limited resources to achieve the greatest impact, what actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?

A Concise Answer:

For all areas where 21 *CFR* 211.22(a) (Responsibilities of quality control unit)[11] **or 21 *CFR* 820.22** (Quality audit)[12] **directly, or indirectly, require that the manufacturers' quality control unit or quality audit unit shall be responsible for approving, or rejecting, materials manufactured, processed, packed, packaged, labeled, tested, quality controlled, or held under contract by another company, the agency needs to take aggressive action to make certain that each manufacturer's quality unit:**

a) **Has appropriate management support, authority, responsibility, and approved standard practices to discharge their second part control responsibility and**

b) **Does, in fact, discharge its responsibilities in a manner that assures that the materials and services comply with all of the applicable requirements of CGMP, the FDC Act** (that regulates foods including dietary supplements, drugs, medical devices, and cosmetics), **the Public Health Service Act** (that regulates blood, tissue, blood products, biological products, etc.) **and all other applicable statutes.**

In the area of drugs, drug products, biologics, and medical devices, the agency needs to require that each firm (manufacturer, processor, packer, tester, quality control agent, holder [or, for goods handled by agents, the responsible agent]):

a) **Validate the quality and compliance of each of its suppliers to the appropriate standards governing that supplier's operation <u>before</u> any lot of material or service is accepted;**

b) **Audit, at least biannually, each of its contracted suppliers of any material or service;**

c) **Track the performance of each of its suppliers with respect to compliance with manufacturing process standards, product quality standards, or service or other standards, as appropriate);**

and

d) Certify to the agency, after initial validation as well as each subsequent audit, that the supplier seems to be operating in compliance with all appropriate statutes and regulations.

Because: a) routine analytical testing and examination cannot determine exactly how a supplier is operating and b) the responsibility for determining that the supplier is producing the product under adequate control is the manufacturers', the manufacturer, processor, packer, packager, labeler, tester, or quality control agent (or if the product is handled by an agent who is not a manufacturer, the agent) must be held responsible for how a material is being made (or, in the case of services, being performed).

Were firms required to do this, the agency could have more confidence in the materials and services supplied. In addition, the inspection burden on the agency could be reduced as the firm's would be being held responsible for validating and auditing their suppliers and the agency would only need to spot check the suppliers.

To make this work, the agency would need to meet the biannual inspection statutes that it is currently deliberately ignoring without counting Preapproval Inspections (PAIs) as "general inspections."

Though the agency may be severely under funded, it first needs to meet its legally mandated inspection windows, then it can worry about which other of its initiatives to address. Based on current realities, the industry is not at all interested in effectively policing itself.

Explanation Of Concise Answer:

The proposal in this area is specifically directed toward those engaged in the manufacture of drug products and devices. However to the extent that it can be applied to other areas that the agency is charged with regulation, the agency should move to amend all of the applicable regulations, including **21 *CFR* 211.22(a)**, to require a quality control unit in all firms and in addition to its other authorities and responsibilities, require:

"The quality control unit shall have the authority and the responsibility for approving or rejecting all materials manufactured, processed, packed, or held under contract by another company and for assuring that the quality standards and specifications meet, or exceed, the minimums established in the manufacturer's approved filing, the CGMP regulations, and the USP compendial standards."

Moreover, while respecting a firm's right to hold its internal audit findings confidential, the agency should require that all external audit records be made available to the FDA for inspection and review. In many instances today, the "manufacturer" is outsourcing one or more aspects of its operations without exerting adequate quality control and the agency knows, or should know, that this is the case.

In drug product instances in which I have been personally involved, the quality control unit of the manufacturer has been prevented from, or restricted in, their release activities for second party operations to the point that the responsible firm's quality control unit had no real approval or rejection authority. This problem is especially significant when, as it has done in many cases,

management has used outsourcing as a means of reducing the quality standards for a product below those originally established for the manufacturer.

In addition, in cases where foreign materials are imported into the US by agents that are **not** registered drug product manufacturers, the FDA should require said agents to **a)** register because they act as the "holders" of the imported materials; **b)** have a quality control unit that meets the same requirements as those for a US manufacturer; **c)** perform in the same manner that manufacturer's are required to.

Should such a course be pursued, the agency would be assured of having a responsible US party to hold accountable if any product was not as it is represented or purported to be.

Because the US firm would be the accountable party, the FDA should be able to reduce the amount of foreign auditing that it is required to do. This would be the case because US firms would seek to use foreign vendors selling to multiple sources both to **a)** reduce their validation and audit costs and **b)** increase their certification comfort. Moreover, there is nothing in this proposal that would forbid the firms from using joint validation and auditing by a competent third party as a means to establish and assure supplier conformity to requirements.

Firms could choose to rely on third-party joint validation and audit of a given supplier or to perform the activity themselves. However, in either case, the complete audit findings, observations information, corrective action plans, corrective actions, and outcomes documents would need to be filed with the agency. The agency would them only need to verify that the validation and audits were competent and did establish that the suppliers and the items supplied were complying by performing random audits on the suppliers.

However, to make this approach work, the agency would need to **a)** assure that all domestic firms had, at a minimum, a biannual general compliance inspection; **b)** inspect all firms seeking FDA-covered approval in a timely manner; and **c)** all foreign suppliers on a random basis such that all foreign firms would be inspected at least once every four (4) years after receiving initial the agency acceptance, relying on the US firms' biannual inspections and annual certifications in place of the mid-term inspections currently mandated. [After all, this proposed system would be much better than the current system that has not been meeting the legislated biannual minimums for some years and, in FY 1999 is only targeted at inspecting less than 25 % of the drug manufacturers.]

Provided the agency took strong action against any firm submitting fraudulent certifications or performing a less than competent initial validation or subsequent audit (or, in the case of consortiums, conspiring to do so) under the debarment provisions, the firms regulated by the FDA should rapidly assume the responsibility for compliance that they should have been doing all along. This should remove "firm not ready" from the list of reasons why a new product is not approved. This should also stop certain firms from using suppliers that they do **not** know are providing the items purchased in a manner that fully complies with all appropriate statutes, regulations, and FDA CGMP expectations. Moreover, by requiring the firms to certify their suppliers, the agency is helping to assure that the items reaching the consumer are as they are represented to be with respect to quality and conditions of manufacture.

Properly implemented, the preceding would be a strong deterrent to certain seemingly violative industry practices:

1. Accepting items with certifications that attest to the product's "quality" [for example, "Lot xxxx is certified as Sulfamethoazole, USP by nnnnnn, qcu title"] that provide analytical test results by the manufacturer that are within the USP ranges but lack any certification that the item was made in a proper environment [that is to say, "made in compliance with drug CGMP as

certified by mmmmm, qcu title; Lot xxxx released by mnmnmnmn, qcu title" or some equivalent statement; typically, the certificate only says, "Released by mmmmmm, qcu title"].

2. Accepting items with certifications that purport to attest to the product's "quality" [for example, "Lot xxx, Sulfamethoazole, USP. Test results certified by nnnnnnn."] but provide analytical test results performed by a third-party laboratory [obviously, the lab, usually lacking access to batch or lot and the site obviously cannot even attest that the batch or lot has the values reported only that the samples did] as requested by the manufacturer that are within the USP ranges and lack any certification that the item was made in a proper environment [typically, "Approved for release by mmmm, lab title"].
3. Accepting items with certifications that purport to attest to the product's "quality" [for example, Lot xxxx, Sulfamethoazole, USP. Approved by nnnn, title] but provide analytical test results performed by a third-party laboratory on samples taken by the exporter [obviously, the lab, usually lacking access to batch or lot and the site obviously cannot even attest that the batch or lot has the values reported only that the samples did and the exporter, lacking any QC unit usually only knows what the test results are — not even whether the lab or the source are operating under appropriate controls] as requested by the manufacturer that are within the USP ranges and lack any certification that the item was made in a proper environment [typically, "Released by mmmm, lab title"].
4. Accepting items without any certifications [a signature without any attestation to the product's standard of quality] that reports product's "quality" [typically, Sulfamethoazole. Checked by nnnnn, title (obviously not a manufacturer's employee)] but provide analytical test results performed by a third-party laboratory on samples taken by the exporter using the USP test methods [obviously, the lab, usually lacking access to batch or lot and the site obviously cannot even attest that the batch or lot has the values reported only that the samples did and the exporter, lacking any QC unit usually only knows what the test results are — not even whether the lab or the source are operating under appropriate controls] as requested by the manufacturer that are within the USP ranges and lack any certification that the item was made in a proper environment [typically. "Released by, m???? (illegible name or initials with no printed name, lab title or, in some cases no title].
5. Accepting items for use in products for human consumption that are less than food grade.
6. Accepting an item with certificates that attest to USP in some sense but are made by a firm that does not even produce a food-grade item.
7. Accepting an item with certificates that do not supply the manufacturers name and address — only that of the supplier.

Though industry does want the FDA to work with it, that same industry is **not** committed to full compliance with existing regulations; is continually lobbying for reduced regulation; and, in some cases, is deliberately operating in a manner that does not meet the CGMP minimums. Until industry becomes proactively committed to full compliance with statutes, regulations, guidance, and recognized standards, the FDA, at a minimum, needs to **a)** thoroughly audit each firm as frequently as it is required to by law and **b)** punish those firms that it finds are knowingly operating in a non-complying mode.

Thus, when in late 1996 [more than 20 years after the current drug CGMP regulations were proposed (1976)] a brand-name OTC product was found to be being manufactured by a non-validated process and have portions of an in-process final blend that are outside of the USP's

lifetime limits, the FDA should have, at a minimum: **a)** forced the firm to recall all batches or seized them because there are competing brand products; **b)** sought the maximum civil penalty from the firm; and **c)** begun an in-depth inspection of all of that firm's products and sites. To the extent that such practices were found to carryover to that firm's prescription drug products or to other locations, the FDA should have sought a consent decree.

After all this firm was knowingly manufacturing and selling adulterated products and had been doing so for some time. Instead, the agency simply issued a warning letter, allowed the firm to take "appropriate corrective action," and permitted existing product to remain on the market. Instead of choosing to protect the consumer from this firm's adulterated product, the agency apparently chose to help the firm protect its market share.

Furthermore, even though, in 1988, the United States Supreme Court in **Berkovitz v. US** (486 US 531, 100 L Ed 2d 531, 108 S Ct 1954) overturned a US Appeals Court decision and ruled that FDA administrators have **no** latitude with respect to discharging their "statutory" duties, the FDA has chosen not only **not** to comply with the FDC Act with respect to the inspection of drug manufacturers but to do so knowingly. When I openly asked a high FDA official at the 23rd GMP Conference in Georgia if the agency was choosing to willfully violate the law, his hesitant response was "yes." The excuse I was given was a lack of resources. When I asked others in the agency, I was told it wasn't about resources — it was simply a matter of priorities.

No wonder the industry sees **no** reason to comply when they see that the agency itself chooses to flout the law. Isn't the survival of the "rule of law" contingent upon both compliance and enforcement by the law keepers?

Furthermore, unless the agency soon becomes a competent enforcer of the statutory requirements, there is little hope that the industry, driven by profit, will be motivated to comply. After all, the agency is inspecting them less, requiring a decreasing level of compliance in certain areas, and many of its personnel are looking to be hired by industry or consultants to the industry in a few years. In addition, many members of Congress look to the industries regulated by the FDA for campaign contributions and, after they are retired or retire, consultant fees. No wonder, the agency's priorities place so little emphasis on regulating the pharmaceutical industry — its not in their best interests to do so.

Instead, we, the external stakeholders, are asked to weigh and balance priorities — many of which have nothing to do with increasing the safety, efficacy or quality of the drug products produced and now marketed directly to us. We are asked to ignore: **a)** the agency's lack of competence and **b)** the pandering of Congress and the agency to the interests of the companies that they are supposed to be regulating.

For myself, the choice of priorities is simple, we need a competent FDA that is capable of doing and motivated to carry out its core mandate — protecting the public. That should be the agency's priority. When that priority is completely satisfied, then and only then, should the question of other priorities arise.

However, given how far the agency is from being able and willing to carry out its core mandate, all other issues should be relegated to a secondary, time permitting, status.

The agency should **not** be about: **a)** reducing the barrier for foreign products so that more jobs can migrate out of the US; **b)** helping industry make a higher profit so that the same medicine can be sold in the EU for half the US price or less; **c)** aiding "health care providers" in committing fraud so long as it is not substantial to increase health care costs; **d)** helping firms

mislead formularies; **e)** approving me-too drug products that offer no therapeutic benefit or continuing to allow products with high risk to be marketed so that firms can continue to compete; f) supporting the education of researchers; or **f)** failing to enforce, or reducing, the quality standards for drug products. If Congress and the public feel that any of the preceding need support, then another agency needs to be funded and these, or any other such priorities, need to be given to it.

As Abraham Lincoln so succinctly put it "a house divided cannot stand." No regulatory agency should be charged with assisting the industry that it is supposed to regulate. The FAA has shown us that trying to serve the public and the airline industry has ended up mostly serving the airline industry and not the public. Hopefully, the agency and Congress will wake up, "smell the coffee," and return the agency's priorities to protecting the public (not the producer) by providing safe foods and cosmetics, safe and effective drug products and devices that have the quality the purport or are represented to have, and actively regulating the industry in a manner that assures that the industry is operating in compliance with all applicable statutes, regulations, recognized standards, guidelines and guidances.

Hopefully, the agency will also wake up, take whatever measures are needed to become competent, and rigorously audit the industries that it is charged with regulating in a manner that makes it more cost-effective for the manufacturers to comply rather than to continues to resist complying.

5. FDAMA requires the agency to continue to meet with stakeholders on key issues. Meetings have ranged from explaining the positions of the agency on particular issues to working with sponsors on product applications. Historically, these interactions have benefited both stakeholders, through better knowledge of FDA, and the agency, by leading to positive changes in its operations.

Agency Question:

Because the agency wants to assure that its stakeholders are aware of and participate in its modernization activities, what additional actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?

A Concise Answer:

If the agency truly seeks to enhance communication processes with all of the stakeholders including the consumers who bears the highest risk and who collectively have the biggest stake, then the agency can accelerate its efforts to make the public aware of the problems it is finding by publishing redacted copies of all FDA Form 483s and Warning Letters to the Internet FOI Reading Room as soon as possible along with the redacted EIRs as they become available.

In addition, the agency should publish (online) and respond to (online) all correspondence that raises a cogent issue or regulatory point so that

all stake holders will be aware of the issue and have access to the FDA's response.

Furthermore, the agency should a) mandate that all future regulations must be drafted and written in simple English at the fifth-grade level and b) undertake an initiative to rewrite all regulations in such simple English rather than the current complex legalistic regulatory language filled with double negatives that is currently used.

Finally, all correspondence to the FDAMA dockets should continue to be made available online in unredacted form.

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"FOOTNOTES"

1. *"In-Process 'Powder' Blend Sampling And Evaluation (And Appropriate In-Process and Final Release Specifications),"* A White Paper, January 1998. [This white paper was submitted to certain key industry, financial, and FDA administrators at the Twenty-Second International GMP Conference held in March at the University of Georgia in Athens, GA; the Agency has agreed to review and comment on, has reviewed and is in the process of preparing a formal answer, and has committed to providing a written response to the key Agency and CGMP-compliance and legal issues raised.]
2. *"Sampling And Testing 'Size,' For In-Process Blends: Legal, Regulatory and Industry Realities, A Call To Action,"* A White Paper, May 1998.
3. "IN-PROCESS FINAL-BLEND SAMPLING AND EVALUATION (AND APPROPRIATE IN- PROCESS AND FINAL RELEASE SPECIFICATIONS), A White Paper, June 1998.
4. "**Scientifically Sound, A Prerequisite For Compliance With 21 CFR 211**," A White Paper, July 1998.
5. "**Formulation Component Complexity**," A White Paper, August 1998.
6. **"PHARMACEUTICAL INSPECTION (SAMPLING & TESTING) VARIABLE PROPERTIES AND INSPECTION FOR COMPLIANCE The Post-Release And The Release Dichotomy,"** A White Paper, December 1998.
7. "PROCESS VALIDATION — ESTABLISHING THE MINIMUM PROCESS CAPABILITY FOR A DRUG-PRODUCT MANUFACTURING PROCESS," A White Paper, January 1999.
8. "GENERATING SCIENTIFICALLY SOUND AND APPROPRIATE ANALYTICAL TEST METHODS FOR VARIABLE FACTORS," A GUIDANCE WHITE PAPER, February 1999.
9. "**HPLC METHOD DEVELOPMENT AND VALIDATION: A Direct Procedure For Determining An HPLC Method's 'Linear Through Zero' Range,"** LC•GC, **17(1)**, 46, 48, 50 (January 1999).
10. **21 CFR 211.165(d)** Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.
11. **21 CFR 211.22(a)** There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
12. **21 CFR 820.22 Quality audit.** Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited. Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.

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Appendix A

A Review of:

The PDA's ***Technical Report No. 25***,

"Blend Uniformity Analysis:
Validation and In-process Testing"

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Paul G. King's
Formal Comments

A Review of:
The PDA's ***Technical Report No. 25***,
"Blend Uniformity Analysis: Validation and In-process Testing"

Review Comments On "1. INTRODUCTION"

While the PDA statement on page S1 in paragraph 2,

"FDA's proposal to amend the CGMP regulations (1) suggests that commercial batch final blends should be routinely tested for active ingredient homogeneity, notwithstanding adequate process validation and other CGMP controls,"

is interesting, it totally ignores that the current regulations, as set forth in **21 *CFR* 211.110(a), that** actually require that each final blend be so tested as apart of the validation of each batch, as follows:

"To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

and it also ignores part of Federal District Judge Wolin's legal opinion (used by the FDA as establishing the minimum that a firm must do for in-process final blend testing) in the ***Barr*** case:

"9. Blend Testing

58. An important aspect of drug manufacturing, blend testing gives firms an opportunity to discover and remedy in-process problems before batches reach the final stages of production. Because finished product testing is limited, blend testing is necessary to increase the likelihood of detecting inferior batches. (1181:1, 1221:2 (Gerraughty)); see also (1036:18 (Bolton) (cannot waive blend content uniformity testing and rely solely on finished product results))."

First of all, one of the two purposes of **21 *CFR* 211.110(a)** is " (t)o assure batch uniformity;" the other is to insure the "integrity" (soundness, conformity to specification) of the drug products. In addition, the written procedures are required to "**describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch** (bolding added for emphasis). Thus, **for each batch**, there must be in-process tests on "**appropriate samples of in-process materials.**" Moreover, these procedures must be established **to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.**"

Because the final blend is, by definition, the last point in the process where an active effort is made to improve the uniformity of the bulk material used in a production process, it is definitely a manufacturing process that is directly "responsible" for causing variability in the characteristics of the in-process material and the drug product (and even the PDA recognizes it as such).

Given that the requisite procedures are required by **21 *CFR* 211.110(a) "to validate the performance of**" the final blend with respect to its variability, the PDA's quoted statement is difficult to comprehend. Because it is, or should be obvious, that the determination of the uniformity of each final blend with respect to its content and any other critical variable factor is a part of the validation of that batch, those that truly believe in adequate process validation would accept it as a given rather than attempting, as the PDA does, to argue that "*routine* final blend evaluation for active ingredient is

unwarranted, although it may be appropriate under certain circumstances" (page S1, paragraph 2, second sentence).

Based on **21 *CFR* 211.110(a)**, "*routine* final blend evaluation" is appropriate and must be done if one is to comply with CGMP and produce batches of drug products that are not adulterated under the Federal Food, Drug, and Cosmetic Act as set forth in **21 United States Code [*USC*] § 351(a)(2)(B)**). Perhaps that is the implicit PDA "circumstance" under which it is appropriate.

Review Comments On "2. COMPLIANCE HISTORY"

Paragraph 1: Agreed

Paragraph 2: Though the paragraph starts out well, it stumbles when it states that the sample size was set at no more than three times the dosage unit weight in Judge Wolin's cited opinion. Attempting to balance the FDA position that a "unit dose" size was required with the industry's position that "it" should be a matter of scientific judgment and the industry's position that a test and two reserve samples is needed for each point (a practice that the Agency did not oppose) Judge Wolin actually said:

> " 64. The Court appreciates the difficulty companies experience taking minute samples from large-volume blends. Indeed, testimony revealed that the smallest thief available can retrieve a 250-milligram sample, (1258:1 (Gerraughty)), so in some cases firms cannot obtain a single-run-weight sample. As such, the Court will follow Dr. Gerraughty's testimony and hold that the appropriate sample for content uniformity testing, in both validation and ordinary production batches, (922:15 (Gerraughty)), is three times the active ingredient dosage size, (921:4, 922:8 (Gerraughty)).
>
> 65. In addition to assuring a more accurate measure of uniformity, this rule accommodates the need for retesting. In order to conduct an initial test and two retests, a standard testing practice in the industry, (671:16 (Mulligan)), analysts need a three-run-weight sample. (671:21 (Mulligan)). Under Inspector's one-run-weight rule, in order to retest the same sample, firms must take additional samples from the same spot in the blend. (681:12 (Mulligan)). Such a requirement would be onerous.
>
> 66. Implicit in the sample size determination for content uniformity testing is the prohibition on compositing multiple individual samples taken from different areas of the blend. Again, in order to detect uniformity problems, firms must avoid this practice which would conceal variations in the blend. (1970:6 (Cooper))."

What was actually said and what was intended is confused because the term "sample size" can have two meanings, (1) the size of the sample taken or (2) the size of the sample tested. In context, it is clear that Judge Wolin's opinion is dealing with the latter (size of the sample to be tested) because it is clear that Judge Wolin's paragraph 64:

> "the appropriate sample for content uniformity testing, in both validation and ordinary production batches, (922:15 (Gerraughty)), is three times the active ingredient dosage size, (921:4, 922:8 (Gerraughty))"

is predicated upon Judge Wolin's paragraph 65:

> "In order to conduct an initial test and two retests, a standard testing practice in the industry, (671:16 (Mulligan)), analysts need a three-run-weight sample. (671:21 (Mulligan))."

Thus, many, including the PDA and the FDA, have obviously misinterpreted and misapplied the ***Barr*** opinion's requirement for "sample size" to mean "the size of the sample collected," when based on the Judge's opinion, "sample size" was intended to mean "the size of the sample tested" —

after all to predict the uniformity of the finished dosage units, none have any trouble agreeing that the size of the samples tested must be no larger than that of the dosage units.

Discussion of the FDA's application of the Wolin decision (beginning on S1 and ending on S2):

The PDA's portrayal of the guidance provided is, in general, accurate and the guidance itself is scientifically sound and appropriate with respect to:

1. Requiring that the sampling should be from the entire batch including dead spots.
2. Permitting the collection of larger samples for further sub-sampling by the laboratory to achieve a proper weight for the *tested* ample size provided the larger blend samples are handled in a manner that prevents further mixing or demixing.
3. Realizing that the acceptance criteria for the blend must be inside of the USP's content uniformity specifications for the drug product.
4. Recognizing that subsequent storage and processing steps cause increased variability in the blend and in the dosage units produced from the blend.
5. Recognizing that blend acceptance criteria outside of the USP Assay limits (miscast as the "composite assay specifications for the finished product") are of regulatory significance.

However, the guidance is not entirely scientifically sound when it:

1. Allow a test sample size larger than "1X" the dosage unit's weight <u>when the "1X" size should be the upper bound for the size of the sample that is tested</u>.
2. Arbitrarily sets a minimum of "at least 10 samples" when that number should be established during process development and should depend on the variability of the final blend with more samples being required when the final blend is, because of the process, equipment, formulation, or some combination of the preceding factors or other factors, less homogeneous and less when development fins that it is highly homogeneous
3. Establishes an arbitrary specification range, the USP's Assay range for samples from any homogenized set of 20 tablets (miscast as the "composite assay specifications for the finished product") and RSD ("4 to 5 %" for all blend samples).
4. Fails to require that specifications established have been proven to assure, with a high degree of confidence, by the use of the appropriate statistical procedures addressing samples from a non-discrete population, that all of the dosage units produced from the final blend, not 95 %, will meet their appropriate <u>batch</u> release specifications and are predicted to satisfy the USP's lifetime requirements that any article at any time will, if properly stored, meet the USP's acceptance criteria when tested.

Page S2, Paragraphs 1 and 2 (after the third bullet's text ends):

Taken together, these paragraphs contain little of substance and are, at best, filled with glib half truths and confounded premises. Further, if what is meant by the report's statement:

"Larger samples than unit dose can be justified"

is that the testing of unbiased blend aliquots that are materially larger than the final dosage unit's size can, on a scientifically sound basis be justified for blend uniformity determination at the "unit dose" level, their premise is patently false.

Because of the truth of the preceding, the testing of unbiased sample aliquots of the final blend at any multiple (2x, 3x, ...100x) of the finished dosage unit's target size masks the

non-uniformity of the blend and should not be done. In my personal experience, involving blends containing between 0.05 % and 80 % active, the following apply:

1. For uniform blends containing 20 % or greater active, the appropriate blend test aliquot size (to be removed from larger blend samples by appropriately skilled analysts) is that **fraction** (from about 0.1 to about 1) of the unit dose weight from which the final sample can be prepared without the need for a dilution step (in one case, 1/10 unit-dose weights sampled from "100X" blend samples of a product containing 50 % active were found to provide the same predicted dispersion values as 1X weights that required 5X dilution and a reduced injection volume to position the samples' responses within the validated linear-through-zero range for the method being used). For the materials typically handled, the true limit is that the aliquot must weigh at least 25 mg, and preferable 50 mg, to assure that the handling and weighing errors do not significantly bias the results.
2. For uniform blends containing between 5 % and 20 % active, the appropriate test aliquot size (to be removed from larger blend samples by appropriately skilled analysts) is between about 0.5 and 1X the unit-dose size (the exact value needs to be determined in development).
3. For uniform blends containing between 0.05 % and about 5 % active, unit-dose-size aliquots should be used.
4. For non-uniform blends, regardless of the level of the active, the test sample aliquots should be weighed at their unit-dose weight and carefully prepared by a schema that minimizes the errors introduced by the dilution procedures used.

Page S3, Paragraph 1:

Given the PDA's and some in the Agency's lack of understanding and acceptance that validation is a journey and not a destination or that **21 *CFR* 211.110(a)** requires validation for each batch, it is difficult for me to comment on the statements made other than to reiterate that **(a)** validation is a journey and **(b) 21 *CFR* 211.110(a)** requires that that journey includes assuring the uniformity of each batch by the testing of appropriate samples of each final blend for their variability.

The current problem, as I see it, lies precisely in the "critical issues" factors that impact mixing alluded to in this paragraph. Unlike the "controlled" picture painted by the wordings used, the realities are:

1. Most firms lack comprehensive ingredient physical specifications that truly control the quality of the ingredients to the point that their variability or variability interactions can have no significant impact on the uniformity of either the final blend or the finished dosage units produced from that final blend. Moreover, many firms do not truly have ingredient controls because the contract between the supplier and said manufacturers does not require the supplier to provide material that fully complies with all the dosage-form manufacturers' established specifications.
2. Typically, the physical specifications for those ingredients that have such are either incomplete, too broad, or otherwise deficient from a control point of view. [Often, they are simply based on 110 % or 120 % or even 150 % of the range (typically, the ranges are widened to accommodate the possibility that future batches might not meet previous and current batches ranges) of values observed for typical materials in commerce (with little or no regard to the tolerances needed to assure that ingredient variation can have no significant adverse impact on the final blend's uniformity). In some cases, though a given physical property has a range of values, the specification is simply set as an upper or a lower limit or a gross range without regard to the distribution of values in the material.]

3. Often the test methodology used is deficient because it **(a)** does not test a truly representative sample, **(b)** tests the sample in a manner that distorts its true properties, and/or **(c)** significantly alters the properties of the material while the test is in progress.
4. Many firms do not even have valid vendor qualification/certification programs because such require preaudit survey, pre-qualification on-site auditing and periodic site auditing in addition to the cross checking of results (as mandated by the CGMP regulation). Moreover, because only a fraction of the containers are sampled, there is little assurance that the samples or the results obtained are representative of the lot. Thus, with a few exceptions, most vendor qualification/certification programs do not and cannot adequately measure, much less, control the true value dispersion for the ingredients purchased. Finally, most such programs are deficient because, in the main, the contractual requirements between the supplier and the manufacturer fail to contain any, much less all, the requisite binding physical-property specifications for all the material supplied to the firm.
5. Most equipment qualification, maintenance and calibration programs neither adequately control the performance of the equipment nor properly account for the surface wear. [For example, though initially well qualified and verified to meet the supplier's specifications and tolerance, a Marion "ribbon blender" having overlapped offset blades continues to be used even though its original cross-sectional "U" shaped surfaces have been worn to the point that its general cross-sectional shape more nearly resembles a thermometer bulb than a "U" and its longitudinal surfaces are visibly non-uniform (wavy) in addition, though the production record does not show it, the operators use stainless steel "paddles" (which they hide when the FDA comes) to aid mixing. The firm's calibration program consists of periodically measuring the shaft rpm when the blended is empty. Recorded maintenance consists of scheduled end seal and packing replace, motor lubrication, and periodic or, failure triggered, blade replacement (additionally, Teflon ® tape is applied before each usage to minimize the leakage around the worn shaft). Even though several process validation studies have been performed, the equipment qualification has not been repeated or verified (because it is obvious that it can't be). In a more subtle case, a Gemco granulation-capable blender was miss-installed in a manner that allowed for the possibility of batch contamination and operated for several months before the error was discovered — equipment qualification? Moreover, the correction was simply described as a refurbishing operation with no record being made of the improper configuration or investigation to determine all the batches that were affected and to ascertain if any of the affected batches were actually contaminated. Even after it was repaired, no valid requalification studies were performed. "Requalification" was limited to verifying that the plumbing as properly installed, the various valves operated properly, a 0.2-atmosphere vacuum was attainable, and that the rotational speed was still within the blender's manufacturer's specification tolerances (no effort was made to check if the surface roughness of surface dimensions met the vendor's specifications — perhaps because of the obvious non-uniform wear patterns on its inner surface?). The "refurbished" blender was then put back into service and additional batches of product were granulated.]
6. The lack of adequately defined and documented blending/granulation processes (reread the preceding example).
7. The lack of adequate control over environmental factors that influence mixing (while most have reasonably adequate temperature controls, many firms, including some of those whose drug product actives and blending processes are significantly affected by humidity, still lack adequate humidity controls).
8. Many change control systems are deficient for one reason or another. Even those programs that do require QCU approval and fully document all changes fail to provide adequate metrics and test results derived therefrom that prove that the process change has had no adverse impact on

the uniformity of the final blend or the drug product dosage units produced from it. [I see no need to bore you with examples because you probably have more in this regard than I do.]

9. The lack of training is so prevalent that even those who supervise and audit production operations, including some FDA inspectors, are not truly competent to perform their assigned functions. Moreover, based on the lack of knowledge of and/or understanding of the CGMP regulations, applicability of the USP's compendial standards, and the appropriate recognized standards, many of the members of the PDA Solid Dosage Process Validation Committee seem to lack appropriate knowledge or understanding in certain of these areas.

Given the preceding realities and CGMP requirements as set forth in **21 *CFR* 211.110**, it would seem that routine blend homogeneity analysis is required as an in-process test even for processes that purport to be or are represented to be well specified, rigorously controlled, and previously validated. Moreover, as the uniformity of the final blend typically limits the quality of the drug product units that can be produced from it, any quality-based firm would, even if it were not required to do so, require that the uniformity of not only the final blend but also of any intermediate blends to be properly established for each batch before committing it to further processing because such firms understand the importance of the key realities that the PDA Committee seems to ignore or, at best, minimize:

For Batches Of Finished Discrete Units

Technical Issues:

1. The sample must be:
   - 1.1 Truly representative of the batch and
   - 1.2 At least the minimum number established by the applicable strictures of the appropriate recognized standards:
     - 1.2.1 For attributes, ***ANSI/ASQC Z 1.4*-1993**, or
     - 1.2.2 For variables, ***ANSI/ASQC Z 1.9*-1993**.
2. The test procedures used must contribute no significant bias to the results for the units tested before valid estimates of the population can be made based on the results obtained for the testing of the fewest number of samples permitted by the applicable standards.

Quality Issues:

1. The results from previous batches cannot guarantee the current batch belongs to the same population as that established by the prior batches — in complex systems, non-obvious upsets and unusual conditions do occur.
2. The sooner a problem is found,
   - 2.1 The less it costs to "fix it,"
   - 2.2 The less the risk is that it will affect the final product, and
   - 2.3 On the human side, the less pressure there is to find some way to ignore the problem and somehow release the batch.
3. Valid "end-product only" discrete-units batch-release inspection (sampling and testing) requires many more samples to be tested than if, at some critical control point, in-process testing has established that the current batch conforms to the "validated" population. [Corollary 1: Compliance of a single article to its USP compendial standard is neither valid nor sufficient for batch release decisions (**see 21 *CFR* 211.165(d)**).]

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For In-Process Contiguous Materials

Technical Issues:

1. The plan for removing materials from the contiguous material must:
   1.1 Take samples that are representative of all portions of the batch and
   1.2 The sampling procedures used must take unbiased samples of sufficient size to permit multiple evaluations of the attributes or variables being evaluated at each sampling point.
2. The plan for testing of the samples removed from each batch must:
   2.1 Take "unbiased" sample-size aliquots from the samples from the material,
   2.2 Take sample-size aliquots from the samples at a size that is no larger than the size of the product units into which the contiguous material is to be made,
   2.3 Use test methods and procedures that contribute no significant bias to the results for the sample aliquots tested before the results obtained can be used to accurately describe the batch's properties.
3. The number of sampling points required to properly describe the batch must be established during the development of the process with fewer samples being needed as the uniformity of the contiguous material approaches absolute uniformity with the fewest number being needed when the contiguous material is a "true solution."
4. For materials in a container, the composition of the contiguous material in the boundary layer between the material and the container's surface differs from the bulk material.

Quality Issues:

1. The samples need to span the batch of materials being tested with the minimum being the top, middle, and bottom of the container that holds the entire batch of material and one sample from as close to the container/material boundary layer as possible.
2. To establish local sample uniformity, at least two (2) and preferably three (3) final-unit-size, or smaller, aliquots should be tested from each sample collected.
3. The optimum point in a process at which the samples should be taken and tested is that at which it ceases to be being made more uniform.
4. If, during development, it is clearly established that there are identifiable areas that always contain the most uniform and the least uniform material, then, though one need to sample from across the batch, a two stage approach can be used for batch evaluation as follows:
   4.1 At Stage One, test multiple aliquots from only the least and most uniform areas. If the results of the testing establish that the results obtained match expectations and predict that the material is acceptably uniform, the batch can be released for further processing or, if the results indicate unacceptable uniformity, that batch can be rejected and an investigation conducted to determine the root cause, or causes, of the failure. In indeterminate cases, Stage Two testing should be done.
   4.2 At Stage Two, test duplicate aliquots from the remaining areas and, as a comparative control, the most uniform area. If the results of the test establish that the results obtained match expectations and predict that the material is acceptably uniform, the batch can be released for further processing or, if the results indicate unacceptable uniformity or are indeterminate, that batch can be rejected and an investigation conducted to determine the root cause, or causes, of the failure.

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5. If, during development, it is clearly established that there are no areas that always contain the most uniform or the least uniform material, one need to sample from across the batch. If the results of the test establish that the results obtained match expectations and predict that the material is acceptably uniform, the batch can be released for further processing or, if the results indicate unacceptable uniformity, that batch can be rejected and an investigation conducted to determine the root cause of the failure.
6. When, for whatever reasons, the batch is transferred from the blender to small hoppers or drums before sampling for uniformity, the following sampling is suggested for initial full-scale validation:
   6.1 At a minimum, take two (2) samples from the bottom of the first and the top of the last container and one from the top, middle, and bottom of all other containers and the results of all samples evaluated by testing duplicate "final unit sized" aliquots from each sample.
   6.2 If the results indicate that the batch is adequately uniform, determine the minimum subsets, including samples from the beginning and end of the batch, that give results that predict adequate batch uniformity.
   6.3 Repeat 6.1 and 6.2 for all of the batches in the validation set and determine if there is any common subset, including the set that is simply the bottom two (2) from the first container and the top two (2) from the last container, that reliably predicts batch uniformity.
   6.4 If there is a common set, that set can be used as the set for "routine" batch evaluations; if there is no common set, then "routine" samples must be taken at all points and tested.

Page S3, Paragraph 2 ("The techniques ...") **Through Page S4:**

Based on the preceding, I see no need to comment further the statements made in this section other than to quote the last sentence in the last paragraph:

"Each company bears the responsibility for its own compliance with applicable laws and regulations."

Review Comments On "3. SAMPLING TECHNOLOGY" (Pages S5 - S10)

The discussion is based on the patently <u>false</u> premise that the manufacturers <u>must</u> take near unit-dose size samples from their blends. As their presentation points out, the only scientifically valid requirement that the Agency can enforce is that the aliquots tested must be unbiased samples representative of the blend whose size must be unit dose, or less, to be truly predictive of the "unit dose" uniformity of the powder blend. The FDA permits any reasonable size samples to be taken (as long as post-sampling handling has been established <u>not</u> to additionally mix/demix them, transported to the laboratory for testing, accurately subsampled at unit size (by procedures that have been established not to additionally mix/demix the sample), and quantitatively tested by validated methods and procedures that do <u>not</u> add significant variability or bias to the values in the aliquots tested.

Based on the realities, the PDA, rather than continuing to waste their efforts on continuing to "prove" that unit-dose sampling is fraught with difficulties (as all know and accept), should focus their efforts on developing and validating procedures for:

1. Training the appropriately skilled personnel for blend sampling, blend-sample subsampling, and subsample testing as well as verifying that each person is competent, does follow the procedures as they are written, takes pride in the quality of their work on an initial and ongoing basis that includes genuine positive feedback for acceptable compliance;

2. Taking the appropriate large-size batch-representative samples and containerizing them in such a manner that their transport to or short-term storage in the laboratory does not significantly mix or demix the samples;
3. Subsampling sample-representative unit-dose-size samples and quantitatively transferring and working them up in a manner that prepares suitable stable solutions for analysis;
4. Calibrating the volume of all Class A glassware at the laboratory's temperature and recording the volume and temperature, tracking the usage of, and using the known volume, corrected for any temperature difference, rather than the "nominal" volume for all Class A volumetric ware used in the calculation of aliquot solution result values.
5. Permitting the rapid analysis of said sample preparations by methods that do not contribute significant variability or bias to the results obtained.

The last time these were issues for me to address, I found the following which might be useful starting points, to be true:

1. The procedures for obtaining valid minimally biased "unit dose" samples from a final blend should be developed and evolved at the same time as the manufacturing process is being developed. (Usually, at the "1 liter" scale, the procedures can be as simple as direct "sampling spatula" scoop sampling from defined locations below the surface if the blend and in the wall area, provided such sampling is done in a properly controlled manner by personnel who are trained in and proficient in performing such sampling.)
2. For large-sized samples, the convenient and appropriate size is about 30 g provided the sample size taken completely fills the container into which it is to be transferred.
3. The best containers to use for powder samples include silanize and unsilanized EPA-clean-grade 20-mL amber or clear glass vials or the similarly clean and treated 30-mL sampling bottles that have been appropriately pre-labeled with the appropriate matching compression-type closures. (My experience is that plastic containers, regardless of their cleanliness or polymeric composition, have not proven to be suitable for large-size powder samples.)
4. The large-size samples should, after being taken from the appropriate location, be immediately transferred into the appropriate pre-labeled container chosen so that the sample aliquots taken completely fill the container (to the extent that there is as little head space as possible), closed, and placed in a bottom-cushioned transport rack into which they just fit in an upright position.
5. After transport to a lab in a manner that minimizes vibration, handle the samples as little as possible.
6. Prior to sampling for testing, the analysts doing the sampling should be pre-qualified using a separate sample of the same blend on being able to take a reliable weight of material using a single scooping of material from various locations in the sample from just below the sample surface and quantitatively transferring it into the initial work up vessel (usually a calibrated Class A volumetric flask of suitable size). (Down to 50 mg, a 5 % relative precision is acceptable; below 50 mg and down to 25 mg, a 10 % relative precision is acceptable; and use of this technique is not recommended below 25 mg.)
7. Using pre-qualified analysts, duplicate "unit size" aliquots (suggested locations: left 0.2-cm down; center 0.5-cm down) are taken and transferred into an appropriately labeled container. (When the testing can validly be restricted to only the most uniform location and the least uniform location, at least triplicate aliquots should be analyzed (suggested locations, left 0.5-cm down, center 1-cm down, and right 2-cm down).

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8. The transferred aliquots are then carefully worked up in a manner that introduces minimal preparation error. (To minimize bias, the standard sample solutions, if required for the test procedure used, should be concomitantly prepared by the same analyst that prepares the samples.)
9. The test equipment and procedures used should be optimized to the point that the variability contribution of the test procedure has been validated and confirmed to be less than 1 % and the maximum method bias is less than 0.5 %. While these limits are easily attained by single measurements when the method is titrimetric and direct UV/Visible, multiple determinations and, in some cases, surrogates and spikes are needed when direct colorimetric procedures or procedures that involve separatory methods (extraction and/or chromatography) are used. (In my experience and understanding as a Ph.D. Analytical Chemist with years of experience in this area, the following apply:
    a. Direct spectrophotometric methods need only make one determination of each of the replicates because that measurement reported is actually the average of (or the equivalent of) multiple measurements;
    b. Titrimetric methods should require at least duplicate measurements (with triplicates preferred) for each aliquot sampled;
    c. Simple separatory methods in general that do not require (notice I did not say specify) the use of an internal standard to track transfer and/or recovery should use a minimum of triplicates with quadruplicates being the recommended number;
    d. For HPLC, GC, CE and similar procedures, the minimums are:
        i. Triplicates for GC and totally thermostated HPLC systems (including preheated mobile phase), and
        ii. Quadruplicates for HPLC systems other that the preceding, CE and similar systems;
    e. For methods "c" and "d," that require an internal standard, at least one more determination than specified for the procedure without the internal standard should be done.
    f. To guard against standard preparation errors, at last two independent standard solutions that span the expected range of specification conforming values should be prepared (typically, at 110 % and 90 % of the sample's targeted level), the higher one used to establish the system's suitability for use, and the lower one's specific response (response/amount) verified as being the same, within experimental error, as the specific response of the higher standard solution before any sample solutions are measured.
    g. To verify that the testing system remains in control, the upper standard periodically measured with a suitable high, low, high set being measured at the end to confirm that their was no significant change in the specific response conformity of the standards over time.
    h. In cases where, for whatever reasons, there is acceptable test system drift, the sample values must be appropriately corrected for the observed drift.
    i. The values used for each sample must be the weight normalized (target weight/actual weight) average of the average responses for each subsample prepared from the samples taken at each location.)
10. The laboratory should be controlled at 20.5 °C ± 0.5 °C and, where possible, all Class A volumetric glassware should be serialized with a minimum calibration requirement that the incoming acceptance calibration screening only accept glassware whose measured corrected volume (contained or delivered) is not larger than the ASTM 1-SD limits for Class A glassware.

Review Comments On "4. DETERMINATION OF AN APPROPRIATE SAMPLE QUANTITY" (Pages S11 - S12)

This discussion simply expands on the false premise of the previous section and contributes little that is helpful to solving the problem of testing aliquots at unit weight.

Review Comments On "5. EVALUATION OF BLEND UNIFORMITY: A STEP BY STEP APPROACH" (Pages S13 - S37)

Though the approaches presented may be of some use and applicability, for the most part they are biased by being grounded in the premise that unit-dose samples **must** be taken directly from the bulk blend. In addition, most of the approaches seem to ignore one, or more, of the following:

1. One or more of the requirements of the CGMP regulations.
2. The reality that the sample values reported are not only biased by the sampling procedures but also by the test procedures used.
3. The USP's uniformity requirements are for:
   - 3.1 Only the dosage units specified in the USP General Chapter and
   - 3.2 Any set of samples in the batch to pass — not for just the one set that is being tested.
4. The minimum number of sampling locations in a contiguous powder batch depends upon the granularity of the powder and the configuration of the vessel, or vessels, from which samples are being taken.
5. For dosage units,
   - 5.1 The units chosen must be truly representative of all of the batch;
   - 5.2 In the United States, the minimum number of such representative dosage units that can validly and legally be used to "determine" the status of a batch based on the testing of variable factors on said representative units for any variable property of the batch (including, but not limited to, Assay, Uniformity and Dissolution) is established by the applicable portions of the controlling standard ***ANSI/ASQC Z 1.9*-1993**; and
   - 5.3 Based on 5.3, the testing of any set of dosage units that is less than allowed by the applicable portions of the controlling standard ***ANSI/ASQC Z 1.9*-1993** is neither scientifically sound nor appropriate.
6. To make a valid comparison between the results from blend testing to those from dosage unit testing, all results must be corrected to the same basis "target unit size" and the number of sample values in each case must be "comparable."

Based on the preceding, those that attempt to make any argument concerning the uniformity of a batch based on the testing of sets of 10 dosage units from batches typically larger than 150,000 dosage units (typically, produced in short runs over a period in processes that do not properly validate that the uniformity of the blend prior to tableting, do not use minimally biased procedures, *etc.*), as some do, have no sound basis for doing so because, in most all cases, the number of samples tested does not meet the applicable strictures of the applicable portions of the controlling standard ***ANSI/ASQC Z 1.9*-1993**. Hopefully, the truly valid standard-complying approaches outlined elsewhere will be helpful here. Moreover, most of the approaches presented blatantly ignore the facts that the representativeness of a sample from a population of discrete units depend upon:

1. The size of the population ($n_{population}$),

2. The size of the sample from the population (n_{sample}), and
3. The complexity or uniformity of the material from which the units are made.

Similarly, for contiguous materials such as dry powder blends, the representativeness of the samples from a given batch requires that the number:

1. Be located in a manner that they span the batch, and
2. Be sufficient to detect the nonuniformity gradients that exist in the material.

Fundamentally, the representativeness of the blend samples also depends on the materials of construction of and configuration of the blend's container, the blending process used, and the complexity and uniformity of the materials from which the blend is made.

Review Comments On "6. CONSIDERATIONS FOR THE ANALYSIS OF BLEND AND DOSAGE FORM SAMPLES" (Pages S38)

Contrary to this section's assertion:

"Testing should be performed by HPLC where possible."

HPLC methods are, in most all cases, the last choice in methods that should be used in determining the uniformity of a batch of tablets or the blends used to manufacture it because of the following:

1. HPLC methods require a significant time to make a single measurement (typically, between 5 and 15 minutes) compared to suitable spectroscopic methods (typically, less than 30 seconds);
2. HPLC systems, because of the injection systems used and the making of measurements in a flowing environment over an extended period of time using detectors with significantly larger biases than the standard UV/visible spectroscopic system, have significantly variability (typically, RSDs for duplicate determinations are about 1 % on average in the best fully thermostated HPLC systems [that many laboratories do not have or use] while the RSDs for the corresponding UV/Visible system are less than 0.1 %); and
3. Because the primary purpose of uniformity testing is to determine the variability of the batch, specificity should only be a secondary issue and, in a properly developed and validated UV/Visible spectrophotometric method using the appropriate short-path flow cell and analytical spectrophotometer having a 3+ Absorbance linearity, the small residual matrix contributions that may be present in spectroscopic measurements made are not an issue. (Moreover, use of the suitable rapid scanning or diode array spectrophotometers, matrix, surrogate, spikes, and deconvolution allow rapid direct measurements to be made even for many of the drugs that contain two active ingredients and those measurements have much less variability and, usually, less bias than the corresponding HPLC methods typically in use in pharmaceutical labs today.)

On the basest level, it would seem that the PDA report is deliberately encouraging the use of HPLC methods, an approach that provides the greatest measurement variability and provides the best *ad captandum* argument for the justification for the testing of an inadequate number of samples. At best, it would seem that those who wrote this report do not understand the capabilities of the available modern computerized UV/Visible spectrophotometric instrumentation systems.

As to the section "Testing should incorporate the following:" the treatment presented is, at best, simplistic and, importantly, neglects to require establishing system suitability before any sample testing is allowed.

Review Comments On "7. EVALUATION OF OUT-OF-SPECIFICATION BLEND RESULTS" (Pages S39 - S41)

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Formal Comments

Whenever I read any discussion of "out of specification" results in the pharmaceutical industry, I am struck by the underlies hypocrisy that underlies much such discussions — if the industry were genuinely concerned about eliminating the root causes of such, they would be operating their inspection (sampling and evaluation or testing) programs in compliance with the requirements of the current ISO/IEC Guide 25 or its superseding current draft as well as establishing standards and controls that would assure the full traceability and substantiation of the validity, or non-validity, of all test results, usual, unusual and "out of specification" OOS.

Were such a test-result traceability and validation program in place, then the report's statement:

> "**Phase 1**: A preliminary laboratory investigation may be useful in determining whether the OOS results appear to be valid based on an assessment of the manner in which the sample was handled and tested by the laboratory"

would read:

> "**Phase 1:** The validity, or lack thereof, of each result, including any OOS result, is established by a review of all the data, ancillary documentation and log books, and controls appertaining thereto, and documentation of the review findings that establish that whether or not:
>
> 1.1 The appropriate methodology and SOPs were used,
> 1.2 The proper volumetric ware and apparatus was selected and used,
> 1.3 The samples and standards were properly handled, weighed, and prepared,
> 1.4 The analysts involved were competent and were operating in control,
> 1.5 The test systems were performing properly,
> 1.6 All procedural steps were adhered to,
> 1.7 The raw data, reports, and results conform to expectations, and
> 1.8 The results, including in the case of the tablets tested individually, the normalized result values, were properly calculated and reported."
>
> Any initial error in the generation of the results related to a failure of the test to conform to its procedural steps shall invalidate all results, without regard to their value and trigger the appropriate corrective actions to generate results that are valid.
>
> Any result for which there is no proof of noncompliance or testing-related error shall be deemed to be valid without regard to whether it is within the range expected, within the limits allowed, or out of its specification limits.
>
> Any proven unexpected result shall, where possible, be confirmed by the appropriate retesting of the sample aliquot tested initially or, when there is one, the reserve aliquot generated concomitantly with the initial test aliquot and properly stored pending test outcome. In such cases, the corresponding aliquot of a passing sample shall be tested concomitantly with the appropriate standard.
>
> When the valid additional testing results agree, use accept initial results with the original then proceed to **Phase 1-A** or **Phase 2**, as appropriate.
>
> When the proven original results and the proven additional results for the unexpected result samples do not agree but they do for the initially passing sample or *vice versa*, take and use the average value as the result value and proceed based on the dictates of the average value.
>
> When neither the original unexpected results nor the expected results in the additional testing set agree with their initial values, within the allowed method's tolerances, but the additional results track the originals, proceed to **Phase 1-A** or **Phase 2**, as appropriate.
>
> **Phase 1-A:** In cases where a proven result is verified to be outside of its expected range or OOS and the property being measured for a given sample is an average property and the original homogenized material or a reserve sample exists, two different analysts shall be provided with the appropriate material

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and independently test the sample. Then, all proven results shall be appropriately averaged and the average used as the value for the sample.

In cases where the retests agree but are significantly (outside of three standard deviations from the aggregate mean value) or one of the analyst's valid results agree with the original value and the other does not (using the same all results average and 3-SD criteria), then the frequency with which that analyst's samples shall contain a check sample shall be increased from the normal frequency to 100 % of the time.

In the case that the results of all analysts disagree significantly and the results for any one are outside of 4 SD from the mean of the other two, the method shall be carefully reviewed for potential weaknesses and all analysts who are currently qualified to perform that method shall have their check sample frequency increased to provide additional assurance that all are operating in control.

Phase 2: When the proven results are not as expected, the investigation shall be expanded to include the sampling and handling procedures used prior to the samples arriving in the laboratory and to the batch itself. (The rest of **Phase 2** is okay except that, if a large body of data is available for multiple batches made using different lots of different raw materials from different sources, the appropriate factor analysis studies should be carried out.)

Phase 3: (The initial paragraph is right on, but the rest needs work.)

The conclusion of this discussion is, except for its reference to using the, at best, suspect approaches presented in the report's Section **4**, to the point and basically accurate.

Review Comments On "8. CONCLUSION" (Pages S42)

The report's CONCLUSION states:

"The PDA Solid Dosage Process Validation Committee recognizes the importance of validating active ingredient homogeneity in the final blend for tablet and capsule products, the final blending process is one in a series of unit operations requiring validation. This report has been prepared to discuss and offer guidance regarding the significant regulatory and technological issues impacting validation approaches and acceptance criteria.

At the present time, the Committee does not believe the recommendations regarding sample quantity and acceptance criteria expressed in the Wolin decision have scientific merit because of accuracy and reproducibility problems inherent in current sampling technology. In addition, because subsequent processing steps often impact the uniformity of the blend, greater consideration should be given to evaluating the totality of the validation to determine the overall acceptability. This involves rigorous evaluation of the content uniformity results for finished product samples representative of the entire batch and, comparison of the consistency of those results to the final blend, and if adequate data is available to product history.

It is apparent from the recent FDA proposal to amend the CGMP regulations that the agency may expect active ingredient homogeneity testing of final blends for routine batch production, notwithstanding adequate process validation and other CGMP controls. The Committee generally does not believe routine final blend evaluation for active ingredient homogeneity is warranted, although there may be appropriate circumstances for its use. In addition, the problems with accurate blend sampling at the unit dose level further exacerbates interpretation of the results.

The Committee hopes this paper provides insight and tools for the validation of final blending processes."

The conclusion starts well enough by properly accepting that "the final blending process is one in a series of unit operations requiring validation." Based on this statement, it is clear that this PDA

Committee accepts, in principle, that **21 *CFR* 211.110(a)** (that requires that there be written control procedures that "describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch " and that those written control procedures "shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product") does apply to the final blends of their tablet and capsule drug products.

However, based on their report, it would seem that they overlooked the fact that the regulations require, among other things, that the procedures "validate" the performance of the final blend process for "each batch."

In addition, the Committee's statement:

> "At the present time, the Committee does not believe the recommendations regarding sample quantity and acceptance criteria expressed in the Wolin decision have scientific merit because of accuracy and reproducibility problems inherent in current sampling technology,"

is, at best, based on a distortion of Judge Wolin's opinion issued in conjunction his decision in the ***Barr*** case.

From my point of view, the Committee has chosen to waste much time and effort in trying to obscure the current CGMP requirements for blend uniformity testing, that even they grudgingly admit do exist by focusing on the problems inherent in sampling large commercial blends containing up to 10^7 units at the "unit dose" level rather than, as they should have, focusing on solving the "problems inherent in current sampling technology" or providing scientific guidance on approaches to collecting valid large-size samples, transporting them, and properly sub-sampling them at the "unit dose" level, an alternative procedure that:

1. The FDA recognizes as being permissible if properly developed, validated and controlled and
2. Does, if done properly, permit the controlled sampling of minimally biased "unit dose" aliquots that can validly be used to characterize the uniformity of the final blends of the powder blends used to make tablet and capsule drug products.

Moreover, their second point, "because subsequent processing steps often impact the uniformity of the blend, greater consideration should be given to evaluating the totality of the validation to determine the overall acceptability" is at odds with **21 *CFR* 211.110(a)** that requires proper controls, and sampling and testing or examination for <u>all</u> "of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

Obviously, the preceding includes a requirement for the rigorous in-process evaluation of representative finished product samples for each batch even though this is not what is typically done. Many firms simply do incomplete "content uniformity only" evaluation of an inadequate number of finished product samples that, as any set, are to some degree "representative of the entire batch" rather than complete evaluation of all the critical variables in the tablet and capsule products (Assay, Uniformity, Dissolution or Drug Release, ...) using sets that have been established to span the entire batch, meet the statistical strictures for representativeness with minimally require that number to be examined meet the applicable requirements of ***ANSI/ASQC Z 1.4*-1993** for attribute examination and ***ANSI/ASQC Z 1.9*-1993** for variable testing.

Moreover, given that each production process for each drug product is supposed to be developed in a controlled manner that establishes the validity of the controls, tests or examinations and specifications appertaining thereto, there should always be a body of data available that establishes the history of each product. Finally, because validation is a journey and not a destination

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and each batch, from the initial performance qualification batch onwards adds to the body of information that defines the process, properly done, each batch is validated and each batch establishes the present validity of the process or the lack thereof.

Contrary to the committee's statement:

> "It is apparent from the recent FDA proposal to amend the CGMP regulations that the agency may expect active ingredient homogeneity testing of final blends for routine batch production, notwithstanding adequate process validation and other CGMP controls,"

the current FDA expectation should be that there be final blend uniformity testing for routine batch production because:

1. **21 *CFR* 211.110** currently requires manufacturers to do it for each batch,
2. Finished pharmaceutical manufacturers are, at a minimum, required to operate in full compliance with the CGMP regulations set forth in **21 *CFR* 210** and **21 *CFR* 211**,
3. FDA personnel have no latitude to modify, by interpretation, any clearly written regulation, and
4. Judge Wolin in his Opinion in the ***Barr*** case found that it was a reasonable requirement.

While the Committee is free not to believe that "routine final blend evaluation for active ingredient homogeneity is warranted," **21 *CFR* 211.110** requires the firms for whom most of the Committee's members work to do routine final blend evaluation for all of their finished pharmaceutical manufacturing processes. Since scientifically sound, FDA-accepted, larger-size sampling protocols exist that do permit the sub-sampling of unbiased "unit dose" aliquots, "the problems with accurate blend sampling at the unit dose level" is, or should be, a non-issue.

Finally, regardless of the " *hopes*" of the Committee, this paper provides little insight into and, in most cases, tools that are, at best, of dubious validity for the scientifically sound validation of the final blends of the initial and routine batches of finished pharmaceuticals as required by the current good manufacturing practices regulations as set forth in **21 *CFR* 211.110** when **21 *CFR* 211** was finalized in 1978. In my experience, it does <u>not</u> take firms 20 years to comply with a regulation if the regulated firms are committed to complying. Where there is a corporate will, any and all obstacles will be overcome and ingenious cost-effective ways will be found to minimize the costs of compliance. When an industry chooses to resist complying and the regulatory agency lacks the will or resources to enforce a clear regulation, then the industry erects a body of ingenuous justifications for their willful noncompliance and does all that it can, including spending large sums to influence Congress to go along with the industry's program, to undermine the regulatory agency's ability to enforce that regulation.

Review Comments On "Appendix I. ..." (Pages S43 - S72)

While Bergum's method is interesting and, at first glance, seems to be well thought out, even the FDA had problems accepting the choice of "90 % assurance." However, the approach incorporates several other questionable practices:

Part "a."

1. The method fails to require or address the requirement that the sample be representative of the batch as the CGMP regulations require (it simply requires "a. Data from a random sample of the product"). [**Sec. 211.160 General requirements, (b)(2), "Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified."**] This omission is crucial because, random

sampling is not valid unless the regions of non-uniformity are randomly distributed which, because regions of non-uniformity are usually associated with some certain location or locations within the blender used, is not the case for blends.

2. The method presumes that having more than 5 % of the samples in the batch fail to meet the USP criteria is acceptable. For tablets, where the simplistic limit that no more than 1 in 30 (3.3_{333333} %) can fail, it should be obvious that a 95 % passing is, on its face, an inappropriate choice. Moreover, because the failing units cannot be presumed to be uniformly distributed, the maximum allowable percentage failing for tablets would have to be less than 0.5 % to assure, with certainty, that any set of 30 tablets, if tested, would meet the full USP content uniformity requirement. For capsule-type products, where the simplistic limit is not more than 3 in 30 (10 %), a 1 % level of failing samples might be good enough to assure that any set of 30, if tested, will comply.
3. As the FDA rightly observes, regardless of the PDA's protestations and hand waving, a 90 % assurance level is not adequate.
4. While, with improvements to properly address the issues in points **1** through **3,** the method may be applicable to blend samples, the procedures outlined in ***ANSI/ASQC Z 1.9*-1993** for variables should be used for evaluations of the dosage-form units.
5. Given the requirements of **21 *CFR* 211.101(a)**, blend mean values from the testing of a valid number of representative samples having minimal sampling and testing bias and/or uncertainty, mean values outside of from about 95 % to 105 % of their targeted value cannot be acceptable.

Part "b."

1. Because the second part of the approach ("b. Data from a nested sample of the product") also lacks a "representativeness" requirement, it too is fundamentally flawed.
2. Similarly, the 90 % assurance and 95 % passing levels are not adequate.
3. Notwithstanding the preceding, because of the CGMP requirements in **21 *CFR* 211.101(a)**, **means** outside of 95 % to 105 % of the powder blend's target are certainly not acceptable. Therefore, at a minimum, the tables should have no entries for those locations where the "predicted" mean range is outside of the range from 95.0 % to 105.0 %.

Review Comments On "Appendix II. ..." (Pages S73)

The SDPI approach is suspect precisely because it totally ignores the mean, assumes, in practice, that n=10 is acceptable because it is a USP number and that the USP's 6.0 RSD is an acceptable limit value. Moreover, because it places no restrictions on the locations for the results or the representativeness thereof, the approach is at best incomplete. Also it seems to rely on the same inadequate level of assurance, 90 %, and percentage passing, 95 %, values as the Bergum Method. (**See** discussion of the SDPI approach on pages S19- S22.)

While the amount of active in the blend is, in general, neither enhanced or diminished by additional mixing, the location-related "assay" values are obviously affected by mixing or else the blend would never become more homogeneous than it was when the active was added initially. Therefore, the divergence of the measured mean at each location from the expected values can be a critical parameter and, as the previous method recognizes, the divergence of the location means from the global mean, even in the cases of sampling bias, is a critical parameter. Therefore, the author's

stated premise that the measured mean potency "is not a critical parameter in the blending operation" (**see** page S22, paragraph 3) is not a valid premise.

Review Comments On "Appendix III. ..." (Pages S73 - 81)

While interesting, because these OC curves are based on the Bergum Method, they suffer from the same flaws that were presented previously n the discussion of Appendix I.

Review Comments On "Appendix IV. FDA Comments , August 29, 1997" (Pages S83 - S87)

1. With respect to the FDA's "A.," I agree with the FDA's concern that the report provided no factual data on "how often firms experience blend sampling problems. ..." In addition, it would be nice if they had provided the procedural approaches that they actually use that cause problems.
2. I also "do not believe it is appropriate to rely on the results of any sampling procedure which is suspected of giving inaccurate results, to validate the blending process. ..." (FDA's "B.").

   Though the FDA's approach is technically correct, I believe that the approach to be used should be developed and validated when the blending process is being developed. In my experience, using the smallest scale at which the mixing can be performed in equipment having the same design as the targeted commercial scale blender (typically, 0.5 cu.ft. to 5 cu.ft.), valid "unit-dose" and larger-dose samples can be taken, the larger-size sub-sampled at the "unit dose," the unit-dose aliquots tested, and the sub-sampling technique can be altered until a reliable sub-sampling procedure can be developed and validated to provide the same results as obtained for valid unit-dose samples tested concomitantly in duplicate, within experimental error. Then, because of the problems that do occur when the blending size is scaled up to the commercial size, the larger-size sampling plan can be used in the full-scale case. Moreover, if the firm wishes to use the transfer containers as their control point, then the sampling plan should include a sample from the wall material on the inside of the blender's discharge area after the blend has been transferred as well as from the appropriate locations in the transfer containers (**see** my initial comments).

   Also, when the full-scale blender's size exceeds 30 cu.ft., the sampling plans for confirmation of adequacy of mixing should be moved to sampling from the transfer containers, totes and drums, into which the batch blend is transferred.
3. FDA's "C.":

   FDA's Point "1.": While superficially sharing the FDA's concerns about the Bergum's method and the USP method, mine are at a much more fundamental level, neither approach seems to be valid for in-process blend release; and the USP's compendial standard is for dosage units not "unit dose" blend samples and certainly not the multi-dose blend samples that seem to be being recommended in the PDA's report. Moreover, at the fundamental level, the assumptions of the method are not scientifically sufficient and, on that basis, the method is not, in general, valid.

   FDA's Point "2.":

   While agreeing with the FDA that the 90 % level cannot be justified on a scientifically sound basis, I am concerned about the FDA's choice of 95 %. If a high degree of assurance is what the FDA expects, the assurance level should be at least 97.5 % in the blend case and

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99 % at the finished dosage unit level. In addition, the minimum level for passing the USP's uniformity "any 30" tests, as has been shown previously, must be higher than 95 %. For the USP's "tablets" compendial standard, the minimum passing percentage that can be justified is certainly not less than 99 % with 99.5 % being a better choice. For the USP's "capsules" and "aerosols" compendial standards, up to 3 in any 30 can fail, the minimum passing percentage that can be justified is certainly not less than 97.5 % with 99 % being a better choice.

FDA's Point "3.":

I wholeheartedly agree with the FDA that one " proper measurement for blend uniformity is the uniformity of the distribution of the active ingredient." However, all critical variables must be identified shown to be adequately distributed not just the active or actives in the drug product. Although measuring the actives only may be sufficient in many cases, there are cases (for example, the complex formulations used for many "extended release" products where development has established that the distribution of some other ingredient is critical) in which the distribution of some other ingredient should be monitored.

Even more important than the requested explanation, is the need to justify the use of normal distribution statistics and small sample numbers in cases where it is:

(a) **Recognized** that the blender consists of some areas where it is more difficult to mix the materials than in the bulk of the blend (walls, wells, shielded areas, etc.) and

(b) **Required** to take some samples from each such area.

In such cases, it would seem that the number of samples and locations would need to be expanded to the point that the samples were representative of the blend before it would be appropriate to use normal distribution statistics.

FDA's Point "4.":

I wholeheartedly agree with the FDA's comments here but feel that, as presented in my discussion of Appendix III, that the SDLI method as presented here is even less fundamentally sound than Bergum's method.

4. FDA's "D.": Here the FDA's comments begin correctly enough but ends with an incorrect statement:

"The techniques described in the Technical Report are intended to evaluate the adequacy of mixing of the powder blend by testing the uniformity of the finished product."

In fact, though Technical Report makes allusion to using a comparison of blend results to uniformity results for the finished dosage units, if at all usable, the sampling and testing approaches presented in the Technical Report can only be used for the contiguous blends because:

(a) There is a recognized applicable National standard, ***ANSI/ASQC Z 1.9*-1993, "Sampling Procedures And Tables For Inspection By Variables For Percent Nonconforming,"** (or its international equivalent, ***ISO 3951*-1989**), that should be used and followed for discrete dosage-form units in a batch for any valid statistical quality acceptance or rejection decision concerning a batch;

(b) The USP clearly states that the compendial standards are neither release tests or statistical sampling plans (USP ***General Notices***, under **Test Results, Statistics, and Standards**, ***USP* 23**, page 9, beginning with the second paragraph, "Confusion of compendial

standards with release tests and with statistical sampling plans occasionally occurs"); and

(c) The CGMP regulations require the use of scientifically sound, appropriate suitable statistical procedures for in-process materials and drug products (which tablets and capsules, at some point are) as set forth in **21 *CFR* 211.110(b)** and, for release, **21 *CFR* 211.165(d)** as follows:

(i) Sec. 211.110(b): "Valid in-process specifications for such characteristics (those that require testing or examination to establish that the batch meets its specifications appertaining thereto) ... shall be ... determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications."

(ii) Sec. 211.165(d): "Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels."

As outlined in this Technical Report, it would seem that the Committee is either (a) totally ignorant of or (b), for their own reasons, deliberately chose not to introduce or address the applicable National standard for <u>testing</u> lots of discrete units, ***ANSI/ASQC Z 1.9*-1993**.

5. FDA's "E.": Here the FDA's comments begin correctly enough but become inaccurate when they:

(a) Cast the "where appropriate" as meaning *"optional"* instead of giving it its proper significance *"<u>required</u> unless it can be proven that it is not necessary*," and, worse,

(b) Incorrectly place it as if it ended the second sentence rather than being a part of the third in **§§ 211.110(a)**.

As written, the section states:

"**Sec. 211.110 Sampling and testing of in-process materials and drug products.**

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate: ..."

Subsection (a) makes it an mandatory requirement that, <u>for each batch</u> (end of first sentence), the required procedures shall be established and followed (from first sentence) "to monitor the output and to validate the performance of those manufacturing processes that may be responsible may be responsible for causing variability in the characteristics of in-process material and the drug product." Moreover, one of the two purposes of said requirements is to "assure batch uniformity."

Thus, when the FDA wrote:

"We recommend the more conservative approach that, when adequacy of mixing is a critical factor in a process, blend evaluation generally is warranted, but may be unnecessary under certain circumstances. It is required under 211.110 of the CGMP regulations (where appropriate), on a batch by batch basis, because it is valuable and feasible. Validation and historical results may define where it is appropriate or not appropriate, but a conclusion that no testing is necessary after validation can not be made before validation is completed and historical data is analyzed."

to properly reflect the true requirements of §§ 211.110, they should have written:

"~~We recommend the more conservative approach~~ **The in-process regulations direct that, when adequacy of mixing is a critical factor in a process, blend evaluation** ~~generally~~ **is** ~~warranted~~ **required**~~, but may be unnecessary under certain circumstances~~**. It is required under 211.110 of the CGMP regulations** ~~(where appropriate)~~**, on a batch by batch basis, because it is** ~~valuable and feasible~~ **mandatory to monitor the output and to validate the performance of the blending process because it is known to be a covered source of variability.** ~~**Validation and historical**~~ **Historical results, whatever their source,** ~~may define where it is appropriate or not appropriate, but a conclusion that no testing is necessary after validation can not be made before validation is completed and historical data is analyzed.~~ **cannot validly be used to predict future performance; they can only predict a future probability. Like the flipping of a coin, though the predicted outcome ratio is 50 % heads and 50 % tails, the post-event reality is either heads or tails and no probability applies. Recognizing this, the regulations properly require that each such process be checked to assure batch uniformity at the completion of critical processing steps such as blending.** "

Similarly, the FDA should have paraphrased **21 *CFR* 211.110** as

"21 CFR 211.110 requires in-process controls and tests ... to monitor **the output and to validate the performance of** those manufacturing processes that may be responsible for causing variability ...Such control procedures shall include, but are not limited to, the following, where appropriate: ... (3) adequacy of mixing to assure uniformity and homogeneity."

because leaving out the phrase "to validate" creates the false impression that the existing regulations **(a)** do not address validation or **(b)** implicitly treat validation as a destination rather than, as they actually do, address and treat validation as an ongoing journey.

Finally, with the preceding changes, the last FDA paragraph is correct as written. If a company can truly prove that no possible change in the physical properties or sources of any of the inputs, order of addition, rate of addition, possible undetected deviation from the manufacturing procedures or equipment function, or other such uncontrolled variables can affect the uniformity of blend produced, then, on the grounds that the process step cannot be responsible for causing any variability in the final blend, the firm may skip in-process adequacy of mixing testing on the final blend. However, I have yet to see any such powder blend, semisolids blending, suspension, or liquid for which this is the case though, as implemented, some liquid solution processes do come close.

6. The FDA's closing technical paragraph rightly points out that the sampling and testing plan used to monitor and to validate the blends from routine batches need not be as thorough as the corresponding plan for the initial full-scale validation studies.

Review Comments On "Appendix V. PDA Response to the FDA Letter, October 9, 1997" (Pages S89 - S99)

Rather than spend further time again refuting the many false premises and flaws in the PDA's alleged scientifically valid approaches, statements, findings, assertions, etc., the reader should reread my comments in light of the of the PDA's statements.

However, that being said, I would like to thank the Committee for their statements made on page S98, under "**PDA Response**," paragraph 1:

"We recognize that §211.110 of the CGMP regulations includes, where appropriate, "adequacy of mixing" as an in-process control (IPC). This section also describes testing and examination as a subset of IPCs. These 1978 regulations were promulgated well before FDA interpreted the regulations to require the present form of process validation for solids. IPC testing for blend homogeneity would not

> appear to be warranted where there is adequate process validation. Clearly, IPC testing is not industry practice. Typically the IPC used by the industry includes monitoring and documented batch adherence to the validated blending parameters, as a part of an overall system of CGMP controls; any assay is generally on a composite sample."

Though the first sentence and the second are technically correct as written, the third sentence contains an implicit false PDA premise (one that the PDA repeatedly attributes to the FDA) and which underlies this entire technical report, namely that either the CGMP regulations or the FDA requires full-scale batches to be sampled at about the unit-dose size. Moreover, the PDA conveniently ignores the fact that in 1978 the regulations mandates that each firm have the proper scientifically sound in-process controls including sampling, testing and/or examination of each batch to monitor the output and to validate the performance of manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product including, as the PDA agrees, blending.

Interestingly, the report's next sentence appears to be a carefully crafted legalism:

> "IPC testing for blend homogeneity would not appear to be warranted where there is adequate process validation."

The reader should take carefully note that the Committee chose to use the word "warranted" instead of "required" and to modify it by the equivocal "where there is adequate validation" (made equivocal because nowhere has the Committee defined or even described what constitutes "adequate validation").

Based on **21 *CFR* 211.110(a)**, there is an in-process, each batch, requirement "to validate performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" and the PDA has agreed that powder blends processes may be responsible for causing variability in the characteristics of in-process material and the drug product" Given the preceding, while possible "not warranted," IPC testing for blend homogeneity" is required. Moreover, the validation of the in-process blend process is only "adequate" when the blend is tested for blend homogeneity or blend uniformity or blend adequacy of mixing.

Given the regulation's clear in-process mandates, the PDA Committee's admission that powder blends are variable, and the PDA Committee's following statement:

> "Clearly, IPC testing is not industry practice."

one can only conclude that, if the PDA Committee's last statement is indeed true, the industry is willfully manufacturing drug products by procedures that do not comply with the current good manufacturing practices governing such practices.

Thus, because of the strictures of the Federal Food, Drug, and Cosmetic Act as set forth at **21 United States Code § 351(a)(2)(B))**[1], the Committee is asserting that the industry has chosen to knowingly and willfully manufacture and introduce into commerce drug products batches that are adulterated.

Moreover, the IPC program for final blends that the Committee asserts that the industry has chosen to use:

> "Typically the IPC used by the industry includes monitoring and documented batch adherence to the validated blending parameters, as a part of an overall system of CGMP controls; any assay is generally on a composite sample."

provides no assurance that it is equivalent to the program that the CGMPs have required since 1978.

Finally, in contrast to the Committee, I understand, in the final analysis, that:

1. The need for in-process blend variability testing for each batch should be based on the CGMP requirements set forth in **21 *CFR* 211.110** and the overarching provisions of **21 *CFR* 211.160**,
2. The size of the aliquots tested from the representative samples taken must be not significantly larger than the size of the unit dose,
3. The results of such testing are required to monitor the output and to validate the performance of the blending process.

Nonscientific and nonlegal matters are properly cast in terms of belief; scientific matters and regulations properly belong to the realm of knowledge and understanding. Given the principles of sound science and quality as I know and understand them as well as the requirements of the regulations as I know and understand them, the preceding three points are musts. I leave it to the Committee members to cast their assertions in terms of we "believe" because it is clear that they do not know (or have chosen either not to know, or to feign ignorance of) the clearly written requirements of **21 *CFR* 211.110** and/or of the proper, scientifically sound approaches to treating blend and drug product inspection (sampling and testing) for variability.

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[1] A drug or device will be deemed to be adulterated — if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" **(21 United States Code [*USC*] § 351(a)(2)(B))**.

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Appendix B

An April 3, 1999 News Report

"Huge rise in DTC TV ads in USA following loosening of rules in mid-1997"

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4/8/1999

Paul G. King's
Formal Comments

"Huge rise in DTC TV ads in USA following loosening of rules in mid-1997"†
[SOURCE: posted on Internet and dated April 3, 1999 2:01 AM EST]

Marketletter, March 29, 1999

"Spending on direct-to-consumer advertising in the USA on network TV hit $393.9 million for the year through November 1998, up 152% from the $156.2 million in the like, year-earlier period, according to Competitive Media Reporting, which noted that the US Food and Drug Administration loosened its rules on TV advertising for prescription drugs in the summer of 1997 (Marketletter's Passim).

Spending on spot, syndication and cable TV ads also increased, reaching $49.6 million (up from $34.9 million), $32.8 million ($13.3 million) and $147.6 million ($67.1 million), respectively.

Magazine and newspaper ad spend down

Meanwhile, in the same period through November 1998, spending on magazine ads was $458.5 million, down from $521.7 million a year earlier. Newspaper ad spending fell to $54 million from $83.8 million. Still, some publishers as well as advertisers feel the spending will soon balance out. Print is coming back, though it is unclear as to what extent this will be, noted an article in Advertising Age, which added that while TV is not going away, the pendulum is swinging back towards the middle.

Advertising in consumer magazines fell 2.2% to 7,270.68 pages, according to Publishers Information Bureau, but advertising in some health-related publications - such as Prevention and Men's Health - saw increases in their DTC medicines business. While Time, Newsweek and People saw decreases in their pharmaceutical advertising, Life and some other publications saw rises, which they attributed to the FDA's requirement that TV ads for prescription drugs must refer to more-detailed product information in other places such as magazine ads.

Benefits of print advertising

Print will continue to be part of the mix for smart companies, noted Matt Giegerich of the Quantum Group, which handles advertising for Schering-Plough's Claritin (loratadine), Eli Lilly's Evista (raloxifene) and SmithKline Beecham's Avandia (rosiglitazone). By using print, he said, drugmakers can target narrow segments of the population, while TV reaches the masses.

Mike Guarini, managing director of Ogilvy Healthcare, agreed with the targeted concept, and pointed out that those wanting to provide more detailed information - and those with limited budgets - find print a viable medium. He also agrees with the prediction of balancing out between print and TV spending this year. Ogilvy handles Merck & Co's Crixivan (indinavir) and Propecia (finasteride).

Ken Wallace, Prevention vice president-group publisher, feels that the more universal drugs, such as allergy medications, will probably keep spending more on TV ads because they are looking for a wider range of people. Makers of cardiovascular drugs and cholesterol-lowering medicines may use more print because they are looking for specific audiences, he told Advertising Age.

But DTC ads do not convince consumers

However, consumers are skeptical about most DTC prescription drug advertising, according to a study conducted by CME Health and reported in Advertising Age. The research, conducted to find out what consumers remember and like in DTC ads, found:

- people thought that money is being spent on ineffective messages, with few consumers responding favorably to the advertising for the 18 brands which were in the survey;

- the ads scored a 33% aided-awareness level, with several brands exceeding 60% awareness levels;
- consumers were twice as likely to dislike ads strongly, i.e. 15 of the 18 brands in the survey;
- most DTC ads have little impact on those most likely to buy the products, such as consumers who actually suffered from the ailment the medication would treat or those with a family member who would benefit; and
- patients, as well as the general public, were likely to give the ads a neutral rating, indicating a lack of interest and involvement in the advertising.

While adverts for Prozac (fluoxetine), Viagra (sildenafil) and Allegra (fexofenadine) show that ad spending, coupled with publicity, will generate awareness, Beth Miller, senior vice president-director of CME Health, said that most pharmaceutical companies still have to learn how to develop ads that people like and that will influence behavior."†

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